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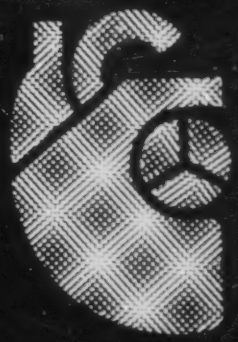

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December 16, 17 and 18, 1985

Division of Heart and
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National Heart, Lung, and
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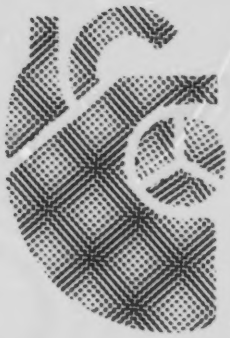

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Meeting Schedule Overview

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AGENDA

1985 DEVICES AND TECHNOLOGY BRANCH CONTRACTORS MEETING

HYATT REGENCY
BETHESDA, MARYLAND

December 16-18, 1985

Sunday, December 15, 1985

7:00 - 9:00 p.m.	Registration Desk Open	Waterford Suite
7:00 - 10:00 p.m.	Social Meeting	Crystal Ballroom Foyer

****

POSTERS AND DISPLAYS — Lalique Suite

Cardiovascular devices on display, Monday and Tuesday

Small Business Innovation Research projects on display, Wednesday

****

THE HASTINGS LECTURE WILL BE PRESENTED TUESDAY MORNING

****

Monday, December 16, 1985

7:30 a.m.	Registration	Waterford Suite
	PLENARY SESSION	Crystal Ballroom
8:00 a.m.	Devices and Technology Branch Program Overview Dr. John T. Watson	
8:15 a.m.	NHLBI Research Training and Development Dr. Donald MacCanon	

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	DIAGNOSTIC INSTRUMENTATION SESSION	Crystal Ballroom
8:30 - 10:30 a.m.	Ultrasound B-Scan Assessment Program	Crystal Ballroom
	Moderator: Dr. Alan Berson	
	Panel Members: Dr. James Toole, Chairman Dr. Gene Bond Dr. Fred Bryan Dr. Barry Goldberg Dr. Daniel O'Leary Dr. Jeff Raines Dr. John Ricotta	
10:00 a.m.	Discussion	
10:30 a.m.	Refreshment Break	Waterford/Lalique
11:00 a.m. - 12:30 p.m.	Plaque Characterization Program	Crystal Ballroom
	Chairpersons: Dr. Fred Forster Dr. Colin Schwartz	
11:00 a.m.	Plaque Characterization by Ultrasound Inverse Scattering Dr. Steven Johnson	
11:15 a.m.	Characterization of Atherosclerotic Plaque With an Intravascular Ultrasonic System Dr. Charles Meyer	
11:30 a.m.	Characterization of Atherosclerotic Plaque Using Doppler-Shifted Signals Dr. John Reid	
11:45 a.m.	Magnetic Resonance Imaging of Atherosclerotic Plaque Dr. Leon Kaufman	
12:00 noon	Plaque Characterization Using Magnetic Resonance Dr. Albert Macovski	
12:15 p.m.	Discussion	

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Monday, December 16, 1985 (continued)

12:30 - 2:00 p.m.	LUNCHEON WITH GUEST SPEAKERS Dr. James Toole Teagle Professor of Neurology Bowman Gray School of Medicine and Dr. J. P. Mohr Sciara Professor of Neurology College of Physicians and Surgeons Columbia University "Research Opportunities in Cerebrovascular Disease"	Cabinet/Judiciary

* *

	BEGIN PARALLEL SESSION A (Session B on p. xxii)	Baccarat Suite
2:00 - 3:15 p.m.	Image Enhancement of Coronary Arteries Program Chairperson: Dr. Otto Schmitt	Baccarat Suite
2:00 p.m.	Computer Enhancement of Intravenous Coronary Angiograms Mr. Robert Selzer	
2:15 p.m.	Temporal Filtration Fluoroscopy/Tomography/3-D Dr. James Nelson	
2:30 p.m.	Image Processing of Coronary Arteriograms Dr. Melvin Marcus	
2:45 p.m.	Visualization of Coronary Arteries and Bypass Grafts Dr. Gabor Herman	
3:00 p.m.	Discussion	
3:15 - 5:45 p.m.	Detection and Quantification of Lesions in Coronary Arteries Program Chairperson: Dr. Otto Schmitt	Baccarat Suite
3:15 p.m.	NMR Methods Dr. Leon Kaufman	
3:30 p.m.	Multiple View, Tomosynthesis X-Ray Method Dr. Albert Macovski	

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Monday, December 16, 1985 (continued)

3:45 p.m.	Refreshment Break	Waterford/Lalique
	Detection and Quantification of Lesions in Coronary Arteries Program (continued)	Baccarat Suite
4:00 p.m.	Multiple View, Dual Energy X-Ray Method Dr. Charles Mistretta	
4:15 p.m.	X-Ray Method With Area Scan and CCD Camera Dr. Theron Ovitt	
4:30 p.m.	Dual View Line Scan and CCD Camera X-Ray Method Dr. Donald Sashin	
4:45 p.m.	Multiple X-Ray DSR System Dr. Erik Ritman	
5:00 p.m.	Synchrotron Generated Monoenergetic X-Ray System Using Energy Subtraction Dr. Robert Hofstadter	
5:15 p.m.	Discussion	
5:45 p.m.	END PARALLEL SESSION A	

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	BEGIN PARALLEL SESSION B (Session A on p. xxi)	Haverford Suite
	BIOMATERIALS SESSION I	Haverford Suite
2:00 - 3:30 p.m.	Physical Trauma to Blood Cells	Haverford Suite
	Chairpersons: Dr. Paul Didisheim Dr. Linda Graham	
2:00 p.m.	Studies of Mechanically Injured Red Cells Dr. Mark Udden	
2:15 p.m.	Red Cells Deformability and Vascular Pathophysiology Dr. Salvatore Sutera	
2:30 p.m.	Flow Effects on White Cell Function and Adhesion Dr. Larry McIntire	

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Monday, December 16, 1985 (continued)

2:45 p.m.	Fluid Shear-Induced Platelet Alterations Dr. Heinrich Joist	
3:00 p.m.	Discussion	
3:30 p.m.	Refreshment Break	Waterford/Lalique
3:45 - 4:45 p.m.	Pharmacologically Modified Surfaces Program	Haverford Suite
3:45 p.m.	A Novel Approach to Nonthrombogenic Polymer Surfaces Dr. Sung Wan Kim	
4:00 p.m.	Heparinized Materials and Blood Interaction Dr. Michael V. Sefton	
4:15 p.m.	Discussion	
4:45 p.m.	END PARALLEL SESSION B	

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6:00 - 8:00 p.m.	Social Hour	Crystal Ballroom Foyer
	BIOMATERIALS SESSION II	Cabinet Suite
7:30 - 10:00 p.m.	Rheologic Contributions to Thrombosis	Cabinet Suite
	Chairman: Dr. Larry McIntire	
7:30 p.m.	Introduction Dr. Anne Ball	
7:40 p.m.	Flow-Induced Near-Wall Excess of Platelets Dr. Eugene Eckstein	
8:00 p.m.	Hemorrheologic Contributions to Thrombosis Dr. George Noon Dr. Ned Hwang	
8:20 p.m.	Blood-Vessel Wall Components in Thrombosis Dr. Vincent Turitto	
8:40 p.m.	Platelet-Endothelial Cell Interactions Dr. Eric Grabowski	

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Monday, December 16, 1985 (continued)

9:00 p.m.	Discussants: Dr. Don Gabriel Dr. Larry McIntire	
	General Discussion	
10:00 p.m.	Adjournment	

Tuesday, December 17, 1985

	BIOMATERIALS SESSION III	Crystal Ballroom
8:00 - 9:40 a.m.	In Vitro Testing of Biomaterials	Crystal Ballroom
	Chairpersons: Dr. Paul Didisheim Dr. Linda Graham	
8:00 a.m.	Surface-Active Antithrombotic Agents for Prostheses Dr. Andrew Lasslo	
8:20 a.m.	A Molecular Approach to Blood Materials Interactions Dr. Robert I. Leininger	
8:40 a.m.	Poly(organophosphazenes) for Biomedical Uses Dr. Harry Allcock	
9:00 a.m.	Cell and Protein Reactions With Foreign Materials Dr. Thomas A. Horbett	
9:20 a.m.	Blood-Materials Interactions: The "Bridge" Problems Dr. W. Jean Dodds	
9:40 a.m.	Refreshment Break	Waterford/Lalique
10:15 a.m.	HASTINGS LECTURE Dr. Adrian Kantrowitz Department of Cardiovascular Surgery Sinai Hospital of Detroit Professor of Surgery Wayne State University College of Medicine "Spectrum"	Crystal Ballroom

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Tuesday, December 17, 1985 (continued)

	MECHANICAL CIRCULATORY SUPPORT SESSION I	Crystal Ballroom
11:00 a.m. - 12:00 noon	Electrically Powered Ventricular Assist Systems	Crystal Ballroom
	PANEL: DEVICE READINESS PROGRAM	
	Moderator: Dr. Frank Altieri	
	Panel Members: Mr. Kenneth Butler Dr. Robert Kung Dr. Peer Portner Mr. Craig Sherman Dr. William Letzing	
12:00 noon - 1:30 p.m.	LUNCHEON WITH GUEST SPEAKER	Cabinet/Judiciary
	Dr. Robert Hofstadter Professor of Physics Stanford University "Links Between Physics and Medicine"	
	MECHANICAL CIRCULATORY SUPPORT SESSION II	Crystal Ballroom
1:30 - 2:10 p.m.	Thermal Energy Ventricular Assist Systems Program	Crystal Ballroom
	Chairperson: Dr. Stanley Briller	
1:30 p.m.	Development of a Stirling Engine-Powered Ventricular Assist System Mr. Maurice White	
1:50 p.m.	Development and Evaluation of a Thermocompressor-Powered Ventricular Assist System Dr. John Moise	
2:10 - 4:45 p.m.	Recent Progress	Crystal Ballroom
2:10 p.m.	Physiology/Pathophysiology of Mechanical Support Devices	
	Moderator: Dr. John T. Watson	
	Speakers: Dr. Larry W. Stephenson Dr. Ray C.-J. Chiu Dr. David Farrar Dr. Laman Gray, Jr. Dr. Mark Levinson	

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Tuesday, December 17, 1985 (continued)

3:15 p.m.	Refreshment Break	Waterford/Lalique
	Recent Progress (continued)	Crystal Ballroom
3:30 p.m.	Cardiac Biventricular Assist and Replacement Devices	
	Moderator: Dr. John T. Watson	
	Speakers: Dr. Yukihiko Nosé Dr. Walter E. Pae Dr. Donald B. Olsen Dr. William C. DeVries	
4:45 - 5:45 p.m.	SPECIAL PRESENTATIONS	Crystal Ballroom
4:45 p.m.	Dr. Peter Frommer Deputy Director National Heart, Lung, and Blood Institute Summary of 1985 Report of the Working Group on Mechanical Circulatory Support	
5:05 p.m.	Professor Barton Bernstein Professor of History Stanford University "The Quest for the Artificial Heart"	
5:25 p.m.	Discussion	
5:45 p.m.	Adjournment	
6:00 - 8:00 p.m.	Social Hour	Crystal Ballroom Foyer

Wednesday, December 18, 1985

8:15 a.m.	Devices and Technology Branch Program Overview Dr. John Watson	Baccarat Suite

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	BEGIN PARALLEL SESSION C (Session D on p. xxvii)	Baccarat Suite
8:30 - 10:30 a.m.	Small Business Innovation Research Program	Baccarat Suite
	Moderator: Dr. Rosalie Dunn	

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Wednesday, December 18, 1985 (continued)

8:30 a.m.	Swallowable Electrodes for Temporary Cardiac Pacing Dr. Robert Arzbaecher
8:45 a.m.	Diastolic Pressure Determination by Phase Discrimination Dr. Kuo-Wei Chang
9:00 a.m.	Adaptive Cancellation in Electrocardiography Dr. Thomas Frank
9:15 a.m.	An Implantable Anastomosis Patency Monitor Dr. David Giuliani
9:30 a.m.	CO_2 Angiography Injector Development Dr. Robert Hirko
9:45 a.m.	Development of Pediatric Catheters That Reduce X-Ray Use Dr. William McCormick
10:00 a.m.	Continuous Monitoring of Doppler Cardiac Output Mr. Stephen Barnes Dr. Paul Jones
10:15 a.m.	Anatomical Substitutes With Proclivity for Cell Lining Dr. Peter Nash
10:30 a.m.	END PARALLEL SESSION C

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BEGIN PARALLEL SESSION D — Haverford Suite
(Session C on p. xxvi)

8:30 - 10:30 a.m. PANEL: MECHANISMS OF CALCIFICATION — Haverford Suite

Moderator: Dr. Suzanne Eskin

Panel Members: Dr. Jane B. Lian
Dr. Robert J. Levy
Dr. Robert D. Cumming
Dr. Mrinal K. Dewanjee
Dr. Hiroaki Harasaki
Dr. James W. Buchanan
Dr. Walter E. Brown

10:30 a.m. END PARALLEL SESSION D

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Wednesday, December 18, 1985 (continued)

10:30 a.m.	Refreshment Break	Waterford/Lalique
	BIOMATERIALS SESSION IV	Crystal Ballroom
10:50 a.m. - 12:00 noon	In Vivo Biomaterials Testing	Crystal Ballroom
	Chairpersons: Dr. Paul Didisheim Dr. Linda Graham	
10:50 a.m.	Hemodynamics in Vascular Surgery Dr. Frank W. LoGerfo	
11:10 a.m.	Must All Implants Elicit a Foreign Body Reaction? Dr. Harvey Sasken	
11:30 a.m.	Endothelial Cell Harvesting for Vascular Prosthetic Seeding Dr. John B. Sharefkin	
12:00 noon	LUNCHEON WITH GUEST SPEAKER	Cabinet/Judiciary
	Dr. Peter A. Jones Director of Basic Science University of Southern California Cancer Center "Molecular Control of Cell Differentiation"	
1:30 - 3:30 p.m.	PANEL: PROBLEMS IN SMALL VESSEL PROSTHESES	Crystal Ballroom
	Moderator: Dr. Linda Graham	
	Panel Members: Dr. Allan D. Callow Dr. John L. Glover Dr. Pierre M. Galletti Dr. William A. Abbott Dr. William E. Burkel Dr. Bruce Jarrell	
3:30 p.m.	Closing Remarks: Dr. John Watson	
4:00 p.m.	Adjournment	

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ABSTRACTS
Ultrasound B-Scan Assessment Program

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RESEARCH TRIANGLE INSTITUTE
UNIVERSITY OF ROCHESTER
JEFFERSON MEDICAL COLLEGE
NEW ENGLAND DEACONESS HOSPITAL
MIAMI HEART INSTITUTE
BOWMAN GRAY SCHOOL OF MEDICINE
B-Scan Assessment Program
CONTRACT NUMBERS: NO1-HV-12917
NO1-HV-12915
NO1-HV-12912
NO1-HV-12914
NO1-HV-12913
NO1-HV-12904

In response to advances made in noninvasive vascular diagnostic instrumentation for the detection and quantification of atherosclerosis, specifically ultrasonic B-Scan imaging, the NHLBI awarded contracts to five clinical, one primate, and one coordinating centers to establish a multicenter program, beginning May 1981, for the detection and quantification of atherosclerosis in carotid and iliofemoral arteries. This 3-1/2-year study hypothesized that B-Scan imaging is accurate in identifying and quantifying localized atherosclerosis, that this accuracy is equivalent to that of angiography when compared to anatomicopathological findings, and is improved by prior knowledge of clinical history and functional studies. This report will concentrate on carotid case results.

After a planning phase and a pilot study, 1,269 cases with B-Scan and angiographic evaluations were enrolled in the main study. Of them, 1,099 (87 percent) were carotid, and 170 (13 percent) were lower extremity cases. The design included two randomizations: (1) 11 percent of the carotid studies were designated for multiple within-center and between-center B-Scan and angio interpretations to assess repeatability/variability (R/V), and 89 percent underwent single interpretations for evaluation of sensitivity/specificity (S/S); and (2) all S/S studies were equally divided (50 percent) between prior knowledge of history and functional data and, blinding from this information, for both performance and interpretation. Relative site of maximum disease, residual lumen, lesion width and characteristics as well as normal dimensions at standard locations were consistently quantified. In the event of subsequent endartrectomies, pathology specimens en bloc underwent similar itemized measurement. Protocols for all study phases were standardized during the pilot study. Equipment used was not identical, but instrument performance was monitored by a dimensional phantom program.

For any disease detected by angiography, B-Scan had a sensitivity of 88 percent, specificity of 50 percent, positive predictive value of 86 percent, and 79 percent overall accuracy. For the detection of >50 percent stenosis by angiography, B-Scan had a sensitivity of 74 percent, specificity of 70 percent, and 72 percent overall accuracy. The overall variation associated with both B-Scan and angiography is comparable, although that of B-Scan is somewhat larger. The review of variance with both techniques indicates that angiography is not a perfect standard against which to compare B-Scan. A similar overall trend in degree of variation was found across centers, but significant degree of variation was found between them. This might reflect population and/or instrument

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differences, but seems to rest heavily on individual operator/reader variability. Knowledge of functional studies prior to B-Scan showed significant improvement in diagnosis of residual lumen, significant stenosis, and total occlusions.

No previous study of this magnitude has reported absolute pathology measurements of carotid atherosclerotic lesion location and extent, in combination with B-Scan and angiography. B-Scan proved to be practical for the detection and quantification of atherosclerosis at the carotid bifurcation. Low specificity of B-Scan versus angiography seems to be caused by disease not easily detected with biplane angiography but readily identified with multiplane B-Scan. The absolute magnitude of B-Scan measurement of lesion dimension closely resembled those obtained with pathology, while angiographic measurements tended to be smaller. B-Scan seems to be better suited for in situ study of arterial wall lesion anatomy, a shortcoming of angiography. As the clinical significance of changes that occur within the arterial wall becomes better understood with further improvement in ultrasonic interpretation criteria and boundary delineation instrumentation, B-Scan imaging will increase in importance as a diagnostic tool.

Fred A. Bryan, Jr., Principal Investigator
James A. DeWeese, Principal Investigator
John Ricotta, Co-Principal Investigator
Barry Goldberg, Principal Investigator
Daniel H. O'Leary, Principal Investigator
Jeff K. Raines, Principal Investigator
James F. Toole, Principal Investigator

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BOWMAN GRAY SCHOOL OF MEDICINE
Ultrasound B-Scan Assessment Program--Animal Models
CONTRACT NUMBER: NO1-HV-12916

As part of the United States Multicenter Ultrasound Assessment Program we evaluated the validity and reliability of B-mode ultrasound in measuring arterial size characteristics of atherosclerotic vessels in animal models. Quantitative data comparisons were made among B-mode and arteriographic images, and pressure fixed gross pathology specimens. Bases on the results of these experiments, the criteria and methods developed in the animal models were extrapolated to high-risk human subjects with asymptomatic carotid artery atherosclerosis.

VALIDITY

B-mode--gross pathology comparisons of lumen diameter in atherosclerotic nonhuman primates were 2.7 ± 0.7 mm (Mean ± SD) and 2.4 ± 0.8 mm respectively, with an absolute difference between the methods of 0.6 ± 0.4 mm (n=200; r=0.41). Similar comparisons of total artery wall thickness were 0.8 ± 0.2 mm and 0.5 ± 0.2 mm respectively, with an absolute difference of 0.3 ± 0.2 mm (n=200; r=0.42). Since considerable learning took place during the course of this study, we also compared lumen diameters between B-mode and pathology for our last series of experiments (n=76 sites). B-mode--gross pathology comparisons of lumen diameters from these subjects were 2.6 ± 0.5 mm and 2.7 ± 0.5 mm respectively, with an absolute difference of 0.4 ± 0.3 mm (r=0.57). Arteriography-pathololgy comparisons of lumen diameters (n=68 sites) were 3.6 ± 0.8 mm and 2.8 ± 0.4 mm respectively with an absolute difference of 0.8 ± 0.5 mm (r=0.75).

RELIABILITY

Reproducibility studies of B-mode ultrasound were done in animal abdominal aortas (n=60) and in human subjects (n=64) who had asymptomatic carotid artery atherosclerosis. First vs second observations of lumen diameter in the monkey models were 2.5 ± 0.4 mm and 2.5 ± 0.5 mm respectively, with an absolute difference of 0.2 ± 0.2 mm (r=0.81). Wall thicknesses of first and second scans were 1.0 ± 0.3 mm and 1.0 ± 0.2 mm, with an absolute difference of 0.2 ± 0.2 mm (r=0.42). In the human subjects with asymptomatic carotid artery atherosclerosis, first vs second observations of lumen diameter were 5.9 ± 1.0 mm and 5.9 ± 0.9 mm respectively, with an absolute difference of 0.4 ± 0.4 mm (r=0.86). Wall thickness measurements of first and second observations were 1.9 ± 0.5 mm and 2.1 ± 0.5 mm, with an absolute difference of 0.2 ± 0.2 mm (r=0.89).

SUMMARY

These results demonstrate that B-mode imaging is (1) a valid method for measuring lumen diameter and arterial wall thicknesses when compared with pathology specimens and (2) a realiable method for measuring lumen diameter and arterial wall thickness in animal models and human subjects.

M. Gene Bond, Ph.D., Principal Investigator
Marshall Ball, M.D., Co-Investigator
Sharon Wilmoth, B.Sc., Co-Investigator
Janet K. Sawyer, B.Sc., Co-Investigator

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Diagnostic Instrumentation

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STANFORD UNIVERSITY/HANSEN LABORATORIES OF PHYSICS AND SCHOOL OF MEDICINE
K-Edge Subtraction Angiography With Synchrotron X-Rays
CONTRACT NUMBER: NO1-HV-38039
GRANT NUMBER: 1 RO1 HL 29824-01A1

The purpose of this program is to conduct an evaluation of tunable synchrotron x-ray beams for use in K-edge digital subtraction angiography of coronary arteries in humans. Activity in the second year has centered on the assembly and test of an x-ray imaging apparatus in a new synchrotron x-ray beam with a horizontal width (12.3 cm) appropriate for human-subject studies.

The initial engineering test of the wide-beam human-subject imaging system occurred in February 1985 and the second in July 1985. These two tests successfully demonstrated the correct operation of all the new system components. The test images obtained with the wide-beam imaging system validate the intrinsic iodine sensitivity, the statistics-limited signal-to-noise ratio, the suppression of soft tissue and bone artifacts, and the spatial resolution of this apparatus. Two further tests, involving the introduction of equipment specifically related to patient studies, are necessary before the first patient examination can occur. The first of these tests involves the introduction of the custom patient chair (deliverable to Stanford in August 1985) and the provision of focusing crystals in the monochromator. The second primarily involves the installation and validation of the patient safety system, but a new beam-chopper capable of the required high switching speeds will also be installed. The first of these outstanding tests is expected to take place in October 1985.

R. Hofstadter, Ph.D., Principal Investigator
E. B. Hughes, Ph.D., Associate Investigator
E. Rubenstein, M.D., Associate Investigator
H. D. Zeman, Ph.D., Associate Investigator
M. Buchbinder, M.D., Associate Investigator
D. C . Harrison, M.D., Associate Investigator
A. C. Thompson, Ph.D., Associate Investigator
G. S. Brown, Ph.D., Associate Investigator

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UNIVERSITY OF PITTSBURGH
Development and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries in Humans
CONTRACT NUMBER: NO1-HV-38041-02

We have undertaken research, development, and clinical evaluation of an improved high-speed system of diode array digital radiography in order to achieve a minimally invasive detection and quantification of atherosclerotic lesions in human coronary arteries. The feasibility of the approach was demonstrated at the University of Pittsburgh under contract to the National, Heart, Lung and Blood Institute. The more advanced system now proposed involves the use of two parallel x-ray beams produced by a dual focal spot tube which illuminates two narrow phosphor screens fiberoptically coupled to self-scanning diode arrays. The output of the diode arrays is sent to a digital computer for processing and display of digital radiographic images of blood vessels containing small amounts of iodinated contrast media as produced in an intravenous injection. As in the earlier prototype, x-rays are collimated to form thin, fan-shaped beams that allow highly efficient rejection of scattered x-rays, thereby maximizing the ability to detect the small amount of contrast media that is found in the intravenously filled coronary arteries. Our digital technique has already allowed us to produce high-resolution images of the rapidly moving coronary arteries from an intra-aortic injection of contrast material, demonstrating the potential of the digital diode technique, which arrests the motion due to the method's millisecond line-by-line exposure. We have also been able to visualize portions of the coronary arteries with an intravenous injection using this technique, but the effects of overlying pulmonary vessels and ventricles prevented us from seeing the entire length of the arteries. In the present system, the use of two closely spaced x-ray beams and solid-state detection systems will allow us to use precise motion subtraction of images. The advantage of using two closely spaced detectors is that we will be able to produce two images in the same heart cycle that are recorded 157 milliseconds apart, which will allow us to remove the fixed structures and vessels in the lung but not degrade the appearance of the coronary arteries. This should be achievable because in the short time between the two images, the coronary arteries move but the pulmonary vessels remain stationary.

During the past year, research, development, and construction of the dual-beam diode array digital radiography system has continued. The U-arm computer control circuitry has been designed and built. The design and construction of the diode array camera, the diode array camera control unit, the control circuits, the handshaking circuitry, and the driver circuits have been completed. The dual-beam diode array system has been installed in an x-ray room at the university hospital and interfaced to our Perkin-Elmer computer and an x-ray generator. The system is now undergoing test pattern and phantom studies. Initial dual-beam digital x-ray images have been produced, and the system is being optimized to further improve the quality of the images.

Donald Sashin, Ph.D., Principal Investigator
Klaus M. Bron, M.D., Co-Principal Investigator

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MAYO FOUNDATION
Quantification of Coronary Artery Stenosis With the DSR
CONTRACT NUMBER: NO1-HV-38042

A major feature of this contract is the replacement of the current Image Isocon based image chains with a charge coupled device (CCD) T.V. camera based image chains. Evaluations of a prototype image chain, consisting of an Oldelft NA 0.48 objective lens, a 75 mm diameter microchannel plate based image intensifier coupled via a 5.6:1 tapered fiber optics bundle to a 384 x 480 element CCD T.V. camera show that the new image chain characteristics meet the proposed needs for intravenous coronary arteriography. Specifically, the noise in the CCD output signal is less than 1 percent at peak signal and is proportional to the square root of the signal and exceeds the estimated x-ray photon noise for the direct beam approximately twofold. Fifty percent of the noise is attributed largely to the scattered x-ray in the image. This is a great improvement on the current Image Isocon based system noise which has noise in the black of at least 1 percent of peak signal. The signal modulation for a 2 mm diameter coronary artery, filled with 1:10 diluted contrast medium (i.e., ~35 mm Iodine/ml), is approximately 30 percent of modulation due to a step change in contrast from water to the diluted medium. The objective lens delivers enough light photons to the first photo electric surface (intensifier) so that one photoelectron is generated for each x-ray photon absorbed by the fluorescent screen. The intensifier/tapered fiber optic bundle system delivers an adequate intensity of light to the CCD T.V. camera to permit full use of the CCD sensor intrascene dynamic range. Provisions have been made to cool the CCD camera sensor with a thermoelectric cooling chip to around 0 °C so as to ensure 1000:1 intrascene dynamic range in the video data. With the successful demonstration of the prototype image chain, we are proceeding to replace all 14 image chains with the new system.

Using this new image chain and rotating the DSR gantry around 360° in 4 seconds, we could simulate a 14 image chain scan, albeit at much lower temporal resolution. With these data, we could demonstrate the main attractions of the tomographic method for imaging coronary arteries following a right sided injection of contrast medium, i.e., the problem of superposition is eliminated and all angles of view are available from a single injection of contrast agent. This was demonstrated with a specially fabricated radiological phantom which is a radiologically life-like chest. The ribs and spine are from a 75 kg male, the heart and lungs are porcine, and the chest wall and upper abdominal contents are made of "dry" water. The left heart chambers, aorta, and coronary arteries contain approximately 1:10 diluted contrast agent so as to simulate the levophase from a right sided injection of 2 ml/kg contrast agent. A 3 mm tract allows a catheter to be advanced from the right axilla via the superior vena cava, right atrium, right ventricle, to the right ventricular outflow tract. The 2 mm lumen of this catheter was filled with 1:10 diluted contrast agent. The brightness of the catheter contents in the reconstructions of this chest phantom exceed the noise in the myocardial region of the reconstruction by at least two standard deviations.

E. L. Ritman, M.D., Ph.D., Principal Investigator
R. C. Bahn, M.D., Ph.D., Co-Investigator
A. A. Bove, M.D., Ph.D., Co-Investigator
P. B. Heffernan, Ph.D., Co-Investigator
R. A. Robb, Ph.D., Co-Investigator
H. C. Smith, M.D., Co-Investigator

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UNIVERSITY OF WISCONSIN
Research, Development and Evaluation of Systems for Noninvasive Detection and Quantification of Atherosclerotic Lesions in Peripheral and Coronary Arteries in Humans
CONTRACT NUMBER: NO1-HV-38043

During the second year of this program we have continued our investigation of digital x-ray techniques for intravenous coronary angiography.

Our basic imaging mode has been temporal subtraction using cardiac phase-matched masks. Using carefully adjusted x-ray beam attenuators and a more carefully controlled animal preparation protocol, we have consistently achieved image quality equal to the best images obtained during the first year.

Simultaneously opacified pulmonary vasculature continues to be a serious source of image degradation. Temporal domain pattern recognition techniques have been used in an attempt to selectively suppress these structures while leaving coronary vessels unaltered. Some progress has been made using parametric correlation images as templates for image modification on a pixel-by-pixel basis. Programs are being developed for simultaneous use of parametric images showing the degree of correlation between individual pixels and reference regions over the pulmonary vein and aorta.

Investigation of dual-energy techniques has begun. In an attempt to reduce the noise in the high-energy image a dual-television aperture technique was tried. Using a television aperture modified to switch 2 F-stops at a 30 Hz rate, we implemented a mode in which a factor of four greater intensity was detected during the high-energy exposure. Although this reduced noise, signal was sacrificed because decreased filtration led to a degradation in the spectral separation of the two beams.

Low-pass filtration of the high-energy image using kernels of between 5x5 and 10x10 has appeared to improve image quality.

A dual-energy rotational mode has also been implemented. This was motivated by the fact that S/N is decreased by a factor of 3 behind the iodine-filled ventricle. Rotation of the gantry at 18°/sec along with 33 millisecond energy switching provides a continuous display of 15 energy subtracted images per second. Optimization of this mode will be investigated in the third year of the contract.

Work on an automated beam compensation device is also proceeding. A new printer which will eventually be capable of forming patient-specific cerium attenuation filters in approximately ten seconds has performed successfully in early tests.

Charles A. Mistretta, Ph.D., Principal Investigator

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
NMR Imaging of Human Coronary Arteries
CONTRACT NUMBER: NO1-HV-38044

This project takes advantage of unique features of NMR imaging (MRI) to generate non-invasively maps of human vasculature. In the abdomen, where vessel reconstruction programs have been first developed, we demonstrate vessel cross-section, flow, the presence of plaque and surrounding anatomy. In the heart, the use of cycled multi-section imaging permits us to acquire 10 sections at 5 points in the cardiac cycle, spanning 500 msec, in an imaging time of 35 min. Different coronary vessels are better imaged at different points in the cardiac cycle.

The process of obtaining reliable visualization of the coronary arteries has been aided by the development of data acquisition software and whole-body antennas that result in a doubling of signal-to-noise levels. An added important factor has been the elimination of gaps between sections. Before these improvements we could visualize the root of the RCA in 3/4 of the subjects. Now we routinely image up to 10 cm of linear length of that vessel. Patients undergoing angioplasty and receiving bypass grafts are being studied with the new techniques. In these patients conventional angiography is available for correlations. Three such patients have been imaged since the upgrade of the unit, with excellent results.

Leon Kaufman, Ph.D., Principal Investigator
Lawrence E. Crooks, Ph.D.
James D. Hale, B.S.
Gary Caputo, M.D.
Charles B. Higgins, M.D.

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STANFORD UNIVERSITY
Visualization and Quantitation of Coronary Arteries Using
Multiple-View Energy Subtraction Digital Radiography
CONTRACT NUMBER: NO1-HV-38045

A system of dual energy tomosynthesis has been implemented and tested. A sequence of dual-energy pairs are taken at different angles using cardiac gating. These are processed and combined to form images of desired planar sections containing the vessels of interest. Our digital fluoroscopic system has been upgraded to enable the acquisition and storage of many dual-energy pairs using ECG gating where the gantry is rotated and the angle encoded for each acquisition.

We have been addressing a variety of relevant problems. The tomosynthesis operation involves selective filtering where objects removed from the vessel plane are blurred. The larger bones are blurred but continue to limit the dynamic range of the image, preventing adequate windowing of the vessels. To counteract this problem, a novel system has been implemented whereby the acquired images are processed such that the bone, at a different plane, is subtracted out, without hurting the vessel image. This has been implemented on phantoms.

Intervening soft tissue is removed by dual-energy subtraction. To minimize the noise in this process, a novel algorithm has been developed that minimizes the squared error between the unprocessed and processed image. This has been implemented with encouraging results.

We are attempting to quantify the stenosis in the presence of low SNR. We model the cross section as an ellipse. Using a few projections at different angles, we estimate the area, eccentricity, and angle of the ellipse. Using simulations, we have achieved excellent results with projections having very low SNR.

Albert Macovski, Ph.D., Principal Investigator

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ARIZONA HEALTH SCIENCES CENTER, UNIVERSITY OF ARIZONA
Research, Development, and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries of Humans
CONTRACT NUMBER: NO1-HV-38046

This paper discusses the status of a novel x-ray imaging device. It consists of a 6-inch diameter proximity focused x-ray intensifier, a modular external CsI sensor, and a coplanar fiber optic taper array for readout of the intensifier by six CCD's. The paper presents images and performance data obtained with a prototype imager which is only 40 mm in diameter and which is read out by only one CCD. In addition, results of a processing algorithm are presented which was developed to detect blood vessels in noisy angiograms.

Theron W. Ovitt, M.D., Principal Investigator
William J. Dallas, Ph.D.
Hans Roehrig, Ph.D., Senior Investigator

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MAYO FOUNDATION
The DSR, Status Report '85
GRANT NUMBER: PO1 HL 04664-24/25

Project I - Show that in children with congenital pulmonary atresia location and area of distribution of pulmonary perfusion by various developmental and surgical systemic to pulmonary arterial shunts can be demonstrated with a single injection of contrast medium into the root of the aorta.

Project II - Potential mismatch between lung geometry and chest wall geometry of dogs with intact chest before and after pneumothorax while maintaining the same intrathoracic air content. Results to date clearly show little change of chest wall (including diaphragm) geometry when prone but marked change in the supine animal.

Project III - Eight human volunteers have been scanned awake, anesthetized, and anesthetized paralyzed. Data analysis from these subjects continues. The data suggest that reduced lung capacity during anesthesia is due to changes in thoracic blood volume, cephalad motion of the diaphragm and/or reduction in rib cage volume.

Project IV - Major improvements in display of organ surfaces (e.g., endocardium or epicardium) have been developed and the algorithms optimized for rapid execution. The addition of color coding to the displays increases the information content of the display.

Project V - The varifocal mirror display system is operational. It is used to display an entire volume image, operator interactive windowing, and related manipulation of the image.

Core A - The DSR scanner maintenance and general refinement of the scanner now enables us to do at least two complex (i.e., up to 20 second) scan sequences per day.

Core B - The ModComp computer system is now being replaced with a (Charles River Data Systems) Motorola based 68000 microprocessor system (coupled to an array processor) for a fourfold increase in reconstruction speed.

Core C - The image analysis programs developed on the Cyber computer are now being implemented on Charles River System based microprocessors. Several of these workstations are now operational greatly increase data analysis throughput.

Core D - Administrative Support -

Erik L. Ritman, M.D., Ph.D., Project Director
Douglas D. Mair, M.D., Project Principal Investigator
Joseph R. Rodarte, M.D., Project Principal Investigator
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NEW YORK UNIVERSITY
Computational Methods in Cardiac Fluid Dynamics
GRANT NUMBER: 2 R01 HL 17859-10A1

The goal of this project is now the development of a three-dimensional computer model of the heart. Once this model is developed it will be used in studies of normal function, pathological function, and for the design of prosthetic heart valves. For example, we plan to study the normal development of the heart and the fluid dynamics of congenital heart disease, and we plan to use the computer model of the adult heart as a test chamber for the optimal design of prosthetic heart valves. (Such an optimal design study in our already-operational, two-dimensional computer model resulted in a new valve design, which is an improved valve of the butterfly-bileaflet type.)

The computational method that we are using for the three-dimensional model is similar to the method that we used successfully in two dimensions. The fluid equations are solved by finite-difference methods on a regular cubic lattice. The heart is modeled by a collection of contractile fibers which are immersed in the fluid lattice. The fibers generate forces that move the fluid, and the fibers in turn move at the local fluid velocity. A computational model of the Dirac delta-function is used to spread the fiber forces to the fluid lattice and to interpolate the fluid velocity to the fiber points.

We are now implementing this method on a Cray-1 computer. In the fluid part of the computation we have achieved full utilization of the vector capability of this machine. We expect to accomplish the same for the fibers. Because the problem is too large to fit in central memory, we are developing a program in which the disk is the primary storage medium. The method will be tried out initially on simple, fiber-wound tubes and then on the developing heart.

Charles S. Peskin, Ph.D., Principal Investigator
David M. McQueen, Ph.D., Collaborating Investigator

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BAYLOR COLLEGE OF MEDICINE
Ultrasonic Instrumentation for Cardiovascular Studies
GRANT NUMBER: 5 R01 HL 22512-08

To eliminate the need for intramyocardial transducers in measuring regional left ventricular (LV) function and to estimate the transmural distribution of LV thickening (TH), we are developing an ultrasonic pulsed Doppler instrument which utilizes a single 10 MHz epicardial transducer. LV TH is evaluated by digitally integrating the velocity of myocardial layers passing back and forth through each of eight sequentially range-gated sample volumes distributed across the LV wall. The resulting displacement waveforms represent the amount of TH between the epicardial transducer and each range gate. With the Doppler audio bandwidth extending from 1 Hz to 1 KHz, velocities from 0.08 to 80 mm/s can be processed, and using a four-quadrant zero crossing counter, resolution is 1/8 wavelength or 0.02 mm.

Others have shown using transit-time (TT) crystals that inner wall (ENDO) TH is three to six times outer wall (EPI) TH. Our initial results, however, showed uniform TH with depth near the LV equator and a modest increase with depth (2/1 ENDO/EPI ratio) near the base and apex but with a 1 to 2 mm offset (noncontractile epicardial layer). To find the cause of the disparity, we began several validation and model studies. Frequency response and resolution were measured by aiming the transducer at a target attached by wire to a speaker driven by a variable frequency triangle wave. With this discrete target, the displacement output tracked the target motion to within 0.04 mm with velocities ranging from 0.05 to 50 mm/sec at target distances from 0 (touching) to 4 cm. A deformable target was modeled using a submerged sponge which was compressed by a piston in controlled amounts. Displacement was measured in 1 mm increments from transducers on both sides of the sponge. Even with non-uniform sponges, superimposable displacement versus depth curves were recorded from each side with no offset. We also compared the Doppler method to the TT method in both EPI and transmural measurements of TH in 25 dogs during control, ischemia, and reperfusion with excellent correlation ($r = .98$, slope = 1.04). Since both methods use the same epicardial crystal, any offset will affect both. We conclude that the Doppler method is accurate and compares favorably to the TT method and that the 1 to 2 mm offset is real, is likely caused by the epicardial transducer, and is unrecognized by the TT method. TH may thus be underestimated by TT, especially in the epicardium where the crystals are close together and the damaged zone is a large percentage of the total. Since ENDO TH is determined by subtracting EPI TH from transmural TH, any errors due to the offset cancel.

We have found that the TH versus depth curve varies with location and is modified by ischemia. We hypothesize that these variations relate to local differences in radii of curvature (shape) and to how the radii change during contraction. We are currently working on a thick-walled ellipsoidal model which appears to predict the regional differences we have found.

Craig J. Hartley, Ph.D., Principal Investigator
Mark L. Entman, M.D., Collaborating Investigator
Lloyd H. Michael, Ph.D., Collaborating Investigator
Roberto Bolli, M.D., Collaborating Investigator

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HENRY FORD HOSPITAL, DETROIT
Valve Assessment by Sound
GRANT NUMBER: 2 R01 HL 23669-06

This is a continuing study to explore the possibility that diagnostic information related to valve stiffness may be contained in the frequency content of heart sounds of patients with bioprosthetic valves. Recognizing that vibration of the valve after closure is the primary and initiating source of vibrations productive of heart sounds, it was shown by mathematical modeling that stiffness of the valve is the primary factor that affects the frequency content.

Among 100 patients with porcine valves inserted $\leq$ 6 months, and therefore, considered functionally normal, the frequency content was 60 $\pm$ 17 Hz (mean $\pm$ standard deviation). The frequency content of the first heart sound (57 $\pm$ 14 Hz) did not differ significantly from the frequency content of the second heart sound (66 $\pm$ 18 Hz).

The frequency content of heart sounds produced by closure of 56 porcine bioprosthetic valves was analyzed before removal for spontaneous degeneration (52 valves) or bacterial endocarditis (4 valves). Sounds were recorded at the chest wall, stored on tape, and analyzed with a spectral analyzer.

Sixteen of 23 visibly calcified or palpably stiffened valves had an abnormally high frequency (64 percent sensitivity). Twenty-four of 31 valves that were not stiff had a normal frequency (77 percent specificity). The predictive value of a positive result [true positive/(true positive + false positive)] was 70 percent. These data suggest that sound frequency is a useful noninvasive indicator of valve stiffening.

Among 32 patients with degenerated valves who were followed longitudinally 2 or more years prior to valve degeneration, 14 (44 percent) showed that the frequency increased to abnormal levels at the time of degeneration. Eighteen of 26 (69 percent) showed no change of the frequency at the time of degeneration, and 3 of 26 (12 percent) showed a transient increase of frequency which returned to normal at the time of degeneration (this is unexplained). We have now observed 20 patients with apparently normal valves who have an abnormally high sound frequency. Whether this implies impending valve failure remains to be determined by continuing longitudinal studies.

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UNIVERSITY OF WASHINGTON
Hemodynamics Associated With Atherosclerotic Lesions
GRANT NUMBER: 2 R01 HL 26706-04

Ultrasonic Doppler techniques have provided relatively quantitative methods of noninvasively measuring hemodynamic effects associated with atherosclerotic plaques. There have been steady improvements in the use of these techniques as gains in the instrumentation have been made. However, even with further instrumentation gains, there is a basic lack of understanding of the hemodynamic factors which prevents the accurate interpretation of measured data and prevents the accurate assessment of early disease.

Studies are being performed to improve our understanding of blood velocity characteristics using a versatile pulsatile flow system capable of incorporating a mean flow component and any arbitrary waveform shape for the pulsatile portion. The specific flow situation being analyzed is the flow through asymmetric stenoses modeled as a hemispherical protrusion in a circular tube.

Two basic hypotheses are being investigated. The first is concerned with the scale and stochastic nature of flow disturbances. By quantitatively measuring the scales of the disturbances such as "eddy size" for the periodic wortex shedding and turbulence scales for fully disturbed flow, we are attempting to relate these measures to the severity of stenosis.

The second hypothesis is that the characterization of the hemodynamics necessitates an understanding of the relations between those characteristics, such as scale, and the characteristics of the "input" velocity waveform. Thus, the flow system developed is capable of producing a velocity waveform controlled by an arbitrary input signal in the range of 0 to 25 Hertz.

Previous work with hot-film anemometry is now being supplemented with a laser-Doppler anemometry system acquired with this grant, which is noninvasive and is capable of forward and reverse flow measurements. Thus, this instrument is a tool for quantitative flow measurements and also can be used to evaluate the capabilities of ultrasonic techniques due to its superior capabilities when used with flow models.

Fred K. Forster, Ph.D., Principal Investigator

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UNIVERSITY OF IOWA
Assessment of Passive Myocardial Stiffness
GRANT NUMBER: 2 R01 HL 27035-04

We are using short axis echocardiographic images for the reconstruction of the three-dimensional (3D) geometry of the left ventricle (LV) with the aid of a digital computer. We have assessed the diastolic elastic modulus of the myocardium using the finite element analysis technique together with the reconstructed LV geometry and simultaneous right and left ventricular pressure recordings. In a study conducted on five open-chested dogs, we estimated the elastic modulus of the myocardium using a computer program that closely predicted the diastolic change in LV geometry (expansion). In the analysis after coronary occlusion, it was determined that the elastic modulus value obtained before occlusion was a poor predictor of the actual expansion after acute ischemia. By assigning a higher elastic modulus to the ischemic (dyskinetic) segments, the computer-predicted expansion closely matched the actual expansion. Thus, the finite element analysis of the 3D echocardiographic reconstructions suggests that acute ischemia increases the myocardial passive elastic modulus or in other words, acute ischemia stiffens the myocardium.

We have also used the 3D reconstruction technique on short axis images obtained from a rapid computed tomographic (CT) system. This new system, referred to as Cine CT, acquires tomographic images in 50 msec, effectively freezing the cardiac motion and bringing the excellent spatial and density resolution of CT to cardiac imaging. We have sucessfully obtained 3D reconstructions on eight mongrel dogs and derived the LV mass from the same. Mass derived from Cine CT reconstructions was compared to the actual mass revealing an excellent linear correlation ($r = 0.99$).

During this grant year, we propose to assess the passive myocardial stiffness in the dog model using the images acquired from rapid CT scans. With the excellent spatial and density resolution afforded by this imaging technique, we hope to improve upon our prediction and localization of the ischemic region using the finite element analysis technique. We also propose to use the 3D reconstruction technique on patients undergoing cardiac catheterization in order to assess the accuracy of this technique in a clinical setting.

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UNIVERSITY OF PITTSBURGH
Local Cerebral Blood Flow by Serial CT Imaging
GRANT NUMBER: 2 RO1 HL 27208-04

We are studying the measurement of local cerebral flow (LCBF) by the use of computerized tomography during and after the inhalation of nonradioactive (stable) xenon gas in the baboon. The method has provided LBF information with a relatively high degree of spatial resolution and anatomical correlation.

With the computer, we calculate a blood flow value for each CT volume unit. By reference to a gray or color scale, the computer then produces blood flow maps with high resolution which correlate to anatomical structures. The flow information derived from these maps corresponds to the physiological condition of the subject and has equally good resolution and sensitivity for superficial and deep brain regions. The rapid multi-level CT scanning used in these studies permits examination of blood flow within multiple brain levels during a single 4-6 minute xenon inhalation.

This method has been used to measure changes in LCBF that occur after pharmacologic and surgical manipulation. Blood flow maps are also able to demonstrate progressive increases in local blood flow which result from progressive elevations of $PaCO_2$ as well as regional reductions in flow which result from surgical ablation of perforating branches of the middle cerebral artery.

We have completed a study comparing the xenon gas method and the microspheres method in the measure of LCBF, using the same tissue volumes and under similar conditions. Results of the combined data indicate that an overall association between the methods exists ($P < 0.0005$). Both the validity of the technique and the effect of xenon inhalation on blood flow have been examined.

Our efforts during the last year have concentrated on the development and testing of a reproducible low-blood-flow baboon and dog model. This model allows us to measure simultaneously LCBF in small tissue volumes using the xenon/CT method as well as other diffusible indicator techniques at below and above tissue viability thresholds.

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PENNSYLVANIA STATE UNIVERSITY
Dynamic Radiographic Assessment of Myocardial Function
GRANT NUMBER: 2 ROl HL 27437-04

Regional wall dynamics, wall thickening, and myocardial perfusion patterns provide sensitive measures of ventricular performance and its correlation with myocardial infarction and ischemia. Nevertheless, techniques currently available for obtaining such measurements are often expensive, invasive, or of limited resolution. A new technology (dynamic radiography), based upon the analysis of secondary radiation fields (scattered and fluorescence), for obtaining such data is under development.

Three-dimensional epicardial wall dynamics are measured using a seven-detector array to interrogate x-rays scattered from the epicardial surface. Real time dynamic displays of epicardial surface contours are shown on a CRT screen. Scan times (close-chest canines) from initiation to data display are under 10 seconds. Epicardial surface location is accurate to 0.2 mm (S.D.) and local wall displacements to 0.1 mm (s.D.). Surfaces behind or in front of the cardiac silhouette are located with equal accuracy.

Wall thickness measurements are accomplished with a two-detector array. Radiation scatter is used to measure epicardial dynamics and x-ray induced fluorescence from the blood pool - myocardium interface is used to measure the dynamics of the endocardium. A prototype has been tested on mechanical models and experimental animals (dogs). Measurements of epicardial and endocardial wall excursions and percent wall thickening agree with the results of others.

Myocardial perfusion measurements are also obtained by automated microprocessor positioning of a germanium spectrometer such that its collimated field of view is restricted to tissue locations on the myocardial free wall. Iodine fluorescence measurements are made subsequent to an intravenous injection of contrast agent. Measurements of local static and dynamic contrast distributions have been carried out on mechanical models, excised canine and pig hearts, and in open- and close-chest canine preparations (with and without coronary ligations) to show regional perfusion patterns.

The development of this dynamic radiographic technology should result in a combined diagnostic system capable of measuring submillimeter ventricular wall dynamics, myocardial perfusion patterns, and ventricular wall thickening. Radiation dose levels (<250 mr) are low and component costs (<20K) for the current prototype systems were modest. A new system under construction is expected to reduce the average radiation dose in the heart to under 50 mr.

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Edward S. Kenney, Ph.D., Co-Investigator
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UNIVERSITY OF PENNSYLVANIA
Reconstruction and Display in Tomographic Radiology
GRANT NUMBER: 2 R01 HL 28438-05

This project is a renewal of a previous grant entitled "Computer Technology for Transaxial Tomography". The change in title to "Reconstruction and Display in Tomographic Radiology" reflects a shift in the nature of the proposed work. We propose to cover various modalities in radiology--namely, computerized tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and ultrasound (US)--all of which are tomographic in the sense that they produce images of slices through the human body. "Reconstruction" in the title of the proposal is to be interpreted as the procedure to produce such images from the measured raw data in CT, PET, and MRI. "Display" in the title is to be interpreted as the procedure to put together in three-dimensional (3D)--or (including time) 4D--space the information that exists in the individual slices. In "reconstruction" we plan to concentrate on finite series expansion methods, methods derived from a semi-continuous formulation, preprocessing of incomplete or distorted data, with applications to CT, PET, and MRI. In "display" we plan to concentrate on segmentation (identification of structures of interest, such as specific organs and tumors, in the 3D space) and on rapid display, analysis, and manipulation of the identified structures, with applications to measurement of volumetric changes in soft-tissue masses, surgical planning, radiation therapy treatment planning, and characterization of the normal, ischemic and scarred myocardium. In all cases computer software will be fully developed, implemented, tested, and evaluated, on the kind of computing equipment that is commonly available in radiology departments.

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PENNSYLVANIA STATE UNIVERSITY
Ultrasonic Scattering by Biological Tissues
GRANT NUMBER: 5 R01 HL 28452-03

This project is directed at furthering the understanding of scattering mechanisms of ultrasound in biological tissues. This understanding is crucial to the accurate interpretation of echographic appearance of tissue structures in images obtained by ultrasonic scanners.

Using a computerized experimental system which facilitates rapid data collection, attenuation coefficient and backscattering properties including backscatter at a single frequency (mainly at 7.5 MHz), backscatter over the frequency of 2 to 8 MHz, and intergrated backscatter over the same frequency range have been determined for various bovine tissues such as heart, liver, spleen, pancreas and normal human blood as a function of time during coagulation. In addition, these properties have also been measured for several types of pathological bovine tissues, namely, liver abscess and cardiac lymphosarcoma. Following acoustical measurements, the tissues are examined histologically.

Preliminary results indicate that of the tissues studied, backscatter from liver is the highest while spleen has the lowest backscatter. It is postulated from an examination of the ultrasonic backscatter and histology of these tissues that the dimension of most populous cells in tissues may be the most important factor in determining the ultrasonic backscatter from these tissues. Further, backscatter from solid portion of liver abscess was found to be significantly smaller than that of normal liver whereas cardiac lymphosarcoma typically have a backscatter less than that of normal myocardium.

Results on thrombus demonstrate that backscatter from thrombus of 12 hours old is at least 18 dB higher than that of blood over this frequency range. A comparison to the backscatter of bovine myocardium shows that myocardium is more echogenic than fresh thrombus and is less echogenic than thrombus of more than 12 hours old. Similar results were also obtain for integrated backscatter measurements.

Further studies indicate that ultrasonic backscatter from erythrocyte suspensions and whole blood under uniform flow is proportional to the fourth power of the frequency as predicted by the theory up to a hematocrit of 0.44. It was also demonstrated that ultrasonic backscatter from blood could be affected by flow disturbance.

K. Kirk Shung, Ph.D., Principal Investigator
Terry M. Wilson, D.V.M., Collaborating Investigator
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UNIVERSITY OF MICHIGAN
Automatic Processing of Digital Echocardiography
GRANT NUMBER: 1 RO1 HL 29716-01A1

We have developed and implemented new methods of direct line-mode digitization of two-dimensional echocardiography (2D echo) images. The envelope-detected RF signal is acquired in a digital format for further processing. Using our present acquisition system, we are able to acquire 1 MByte of data in real time over 1 second.

The detection of endocardial boundaries in digital 2D echo is often difficult because of drop-out caused by backscattering of the ultrasound signal in tissue. We tested an algorithm for automatically detecting the endocardial edge in a 2D echo cardiac phantom which consists of synthetic tissue equivalent material containing 16 eccentric annuli of different echogenicity simulating individual frames of the LV short axis throughout a cardiac cycle. Each digitally acquired 2D echo frame was first smoothed by a Gaussian shaped filter, before the first derivative of the image was approximated. Next, nonmaximum values along the direction of maximum gradient were set to zero. The edge points were then found by searching radially from the center point for the maximum gradient magnitude. A total of 360 such points were found for each frame, and each set of data points was approximated by a quadratic curve fitted to the data using the method of least squares. The computed 2D echo diameters and areas correlated well with actual phantom data ($r = 0.9957$ for diameters: $r = 0.9877$ for areas). We have thus empirically validated in this model the feasibility of applying this algorithm to accurately detect endocardial boundaries using directly digitally acquired 2D echo data.

Because we experienced penetration problems with the previous phantom, we are presently constructing a modified cardiac phantom which has a much lower attenuation coefficient. This modified phantom will be used to further validate automatic epicardial border detection. In parallel with this, we have started to acquire digital 2D echo data in open-chest canine models during control conditions, following circumflex coronary occlusion, and then following coronary reperfusion. In addition to 2D echo data, we are simultaneously acquiring high fidelity LV pressure as well as the EKG, aortic pressure, and LV dP/dt during the experimental protocol. We have developed a time code generator to temporally match pressure-2D echo frames for further analysis of pressure-area, pressure-thickness, and pressure-shape change relationships for evaluation of global and regional contractile changes following the interventions. This analysis should provide unique and innovative information concerning global and regional myocardial mechanics during a variety of conditions.

Andrew J. Buda, M.D., Principal Investigator
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UNIVERSITY OF PENNSYLVANIA
Visualization of Coronary Arteries and Bypass Grafts
GRANT NUMBER: 5 R01 HL 29985-03

We are applying technologies which have arisen in computer science and psychophysics to the improvement and evaluation of clinical performance as related to coronary arteries and coronary bypass grafts. Specifically, we are investigating how images from intravenous digital subtraction angiography and from digital subtraction root arteriography can be enhanced and comparing the efficacy for lesion detection and quantitation of the enhanced images with unenhanced images and with those obtained by selective coronary arteriography. The enhancement techniques include the use of standard image processing methods and specifically developed techniques for vessel detection, three-dimensional blood-vessel reconstruction, modeling of myocardial dynamics, medial line representation, lumen size estimation, and display of vessel structure. Our theoretical ideas are being implemented into working software packages, which are then evaluated on images from a swine coronary atherosclerosis model.

Specifically, during the third year of this 3-year grant, we have finalized computer packages for automatic measurement of coronary vessels from digital angiograms and for computer generating masks for an arbitrary combination of cardiac and respiratory phases and subsequent subtraction. The process of artificially inducing coronary arterial disease in swine has continued, and such swines have been imaged. Equipment that has been previously built under the support of this grant has been used to monitor and record the respiratory and cardiac cycles and to correlate them to the imaging process. This information was used in the creation of computer-generated masks. A rule based expert system, called ANGY, for identifying and isolating coronary vessels in digital angiograms has also been developed and implemented. The software packages have been tested on experimental data of (a) contrast filled pipettes, (b) excised hearts with contrast material in the arteries, and (c) DSA of live swine.

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UNIVERSITY OF UTAH
Temporal Filtration Fluoroscopy, Tomography, and 3-D Display
GRANT NUMBER: 5 R01 HL 30001-03

The digital high-pass temporal filter which we have described in past meetings is currently being installed in the University of Utah Cardiac Catheterization lab in parallel with a digital subtraction system (DA-100 HS, Fisher Imaging) to allow comparison of subtraction images with filtration images from an identical set of data.

The work on display of cardiac tomograms on a varifocal length mirror has been suspended. A new method for providing a 3-D coronary angiographic image has been devised by Kruger and will be described in his report.

Recent work has concentrated on analysis of cine and high-pass filtered video images of a coronary artery phantom. Multiple observers estimated and did caliper measurements of well-defined "coronary artery" lesions on simultaneously acquired 60 fps cine and 30 fps high-pass filter video images (interleaved readout) following injection of full strength and half strength Renografin 76. Results of these human estimates and measurements demonstrate a broad inter- and intraobserver variability (20-30 percent) as previously reported (Bray et al., Cathet. and Cardiovascular Diag. 11: 17-24, 1985). Computer algorithms for video densitometric lesion analysis showed markedly improved accuracy and decreased variability. These results will be presented and discussed.

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Robert A. Kruger, Ph.D., Co-Investigator
Bruce E. Bray, M.D., Fellow
David Dedrickson, M.D., Student
Bevan Bastion, Student

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CALIFORNIA INSTITUTE OF TECHNOLOGY, JET PROPULSION LABORATORY
Computer Enhancement of Intravenous Coronary Angiograms
GRANT NUMBER: 5 R01 HL 30010-03

Computer techniques are being developed to enhance images of coronary arteries from intravenous angiograms. The methods include directional hi-pass filters applied to individual cine frames, temporal hi-pass filters applied to adjacent frame sequences, and registration and averaging of in-phase frames in successive heart cycles. Efforts are currently directed toward processing of digital radiographic data provided by Mike Vannier at Washington University in St. Louis using a Siemens Digitron 2 digital angiographic system. Fairly good visualization of the LAD and right coronary artery has been achieved from venous-injection digital angiograms, but efforts to enhance the left main and circumflex arteries have been less successful. The enhancement methods have also been successfully used to improve visualization of coronary arteries from left ventriculargrams.

Robert H. Selzer, M.A., M.S., Principal Investigator
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INSTITUTE OF APPLIED PHYSIOLOGY AND MEDICINE
Pulsed Doppler Imaging of Coronary and Cardiac Dynamics
GRANT NUMBER: 5 RO1 HL 30642-03

The objective of this project is to provide a means for noninvasive assessment of the dynamics of blood flow in the coronary artery tree, coronary bypass grafts, and in the intracardiac channels. To achieve this objective, we are attempting to extend the capabilities of pulsed Doppler ultrasound by developing an ECG-gated, two-dimensional pulsed Doppler sector scanner that will allow online acquisition, storage, analysis, and redisplay of coronary and cardiac dynamics.

Currently we have integrated our multi-gate pulsed Doppler into a static B-arm and have developed scan conversion software to allow display of two-dimensional pulsed Doppler images in a sector format. This allows us to, for the first time, begin to generate tomographic images of flow which, when combined with the ECG gating, allow us to proceed with examinations to detect flow in small vessels in the vicinity of the heart. Our first goal is to examine coronary bypass grafts to determine patency since approximately 20 percent of all bypass grafts occlude within one year of surgery. A noninvasive technique to study bypass grafts for occlusion would be of great benefit to the clinical management of these patients. Previous studies using pulsed and CW Doppler without Doppler imaging have been marginally successful in locating and determining patency of bypass grafts. Such exams are extremely difficult and time consuming since the failure to find flow in the graft in such an examination is not conclusive, because it is possible to miss the region in which the graft is located. This Doppler sector scanner will allow us to more readily determine that we have fully examined the regions where coronary bypass grafts should be found therefore greatly improving the accuracy of this technique.

The current imaging system has a 512 X 512 X 8 bit memory which limits us to 16 frames per heart cycle of 128 X 128 in resolution. The number of frames per heart cycle can be increased from 16 to 32 and resolution increased to 256 X 256 by adding memory to the system. A digital signal averager has been constructed which can perform both spatial and time averaging of signals on the output of the Doppler system. These signals are then fed through direct memory access to the graphic system. Depending upon the rate of line display in the imaging system, this digital signal averager produces an increased signal-to-noise ratio of from 6 to 14 over the previous analog sweep integrator. Logarithmic compression of the signal is also performed to improve the dynamic range of the resultant image.

At this stage, the hardware development has just been completed and we are beginning to acquire images on human volunteers.

John R. Klepper, Ph.D., Principal Investigator
Merrill P. Spencer, M.D., Co-Investigator

UNIVERSITY OF IOWA
Ventricular Phase Imaging Compared to Electrical Mapping
GRANT NUMBER: 1 R01 HL 30936-01

The overall objective of this research is to enhance and validate a radionuclide imaging technique for evaluation of the origin of and subsequent sequence of electrical activation during ventricular pacing or ventricular tachycardia. Our ultimate goal is to determine the usefulness of phase imaging in defining the origin and pattern of ventricular tachycardia patients who are being considered for surgical therapy. In this past year, our work has focused upon the development of alternative image processing techniques for performing phase imaging and performance of initial animal experiments to determine the accuracy of phase imaging.

We have begun to explore patient-specific phase analysis techniques. In contrast to the "conventional" method, this technique approximates the radionuclide time-activity curve with a function derived from the individual patient. This technique requires the use of nonlinear regression methods and, in our present implementation, requires a good deal of computer time. Although our testing of this approach has been limited, it appears to offer some improvement compared to conventional methods. We have also explored a phase analysis technique based upon Walsh-Hadamard transforms. This approach was initially suggested in a published paper in the Journal of Nuclear Medicine. Although this suggestion appears appealing, we have demonstrated that it is of little use.

We have performed two series of dog experiments to begin to validate our phase imaging techniques. In our series, we studied 10 chronic dogs with implanted pacemakers. We injected a small volume of gadlinium-labeled microspheres adjacent to each pacer to serve as a marker. Following phase imaging, the chest was opened and the ventricles electrically mapped. A major finding of this study was that the evaluation of the accuracy of phase imaging was limited by the ability to spatially register imaging and electrical mapping measurements. The use of radioactive markers has proved to be extraordinarily helpful for this purpose, and we are presently developing an objective method of relating imaging and electrical mapping results.

Steve M. Collins, Ph.D., Principal Investigator
James B. Martins, M.D., Co-Investigator
James C. Ehrhardt, Ph.D., Co-Investigator
Peter Kirchner, M.D., Co-Investigator

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DESERET RESEARCH COMPANY--UBTL, INC., DIVISION
Myocardial Salvage With Unloading and Venous Perfusion
GRANT NUMBER: 1 RO1 HL 31215-01A1

Salvage of myocardium may be optimized after coronary artery occlusion with coronary sinus-vein retroperfusion of arterialized blood or in combination with "demand" therapies (IAB, LVB). A complete retrovenous driving system and catheters have been built and tested in sheep and recently in the dog. Catheterization techniques, PTCA balloon occlusion of the left anterior descending coronary artery, and methodologies to determine "area at risk" (Evans-Blue, tetrazolium staining, light microscopy and E/M) have been developed and validated in the sheep and dog. Digital subtraction venous angiograms revealed retrovenously pumped blood and dye in the coronary veins and antegrade in the coronary arteries. Microfil injection studies have been used to document the coronary artery and venous anatomy in both the sheep and dog. The sheep exhibits a high incidence of ventricular fibrillation after distal LAD occlusion in contrast to the dog. Both models are being employed to evaluate retrovenous myocardial perfusion and combined "demand" therapies on salvage of myocardium. This approach to myocardial salvage may provide an effective closed chest therapy in patients with myocardial ischemia and during coronary angiography, thrombolysis, and angioplasty.

Jeffrey L. Peters, Ph.D., M.D., Principal Investigator
Clifford S. Kwan-Gett, M.D., Co-Principal Investigator
Kelly W. Smith, E.E., M.D., Co-Principal Investigator
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Barry L. Bagley, B.Sc., Collaborating Scientist
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John A. Burkart, Ph.D., Biostatistician
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Dennis S. Yutani, M.D., Nuclear Radiologist
Richard D. Strickland, Project Coordinator

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PATHFINDER ENTERPRISES, INC.
CO_2 Angiography Injector Development
GRANT NUMBER: 5 R44 HL 31888-03

Angiography is a highly useful procedure in the diagnosis of many ailments related to circulatory or fluid flow problems in the body. The procedure is minimally invasive and, with the small incisions required, is preferable to diagnostic surgery when the resulting radiograms contain sufficient information. However, standard iodinated contrast materials often cause discomfort and hypersensitivity reactions. Even the new nonionic contrast agents have been shown to cause endothelial damage in patients. On the other hand, carbon dioxide, a substance occurring naturally in the blood, has been shown to possess useful imaging qualities, especially when used in conjunction with digital subtraction x-ray units. Lower, rather than higher, radio-opacity works just as well in an area to be imaged when the background field can be subtracted away electronically. Digital subtraction radiography has improved the image quality obtainable with carbon dioxide sufficiently to compare with the more toxic iodinated contrast agents. Carbon dioxide, used with digital subtraction radiography and a reliable injection system, may come to be used on a routine basis. With its high serum solubility and its ability to combine with alkaline buffers, carbon dioxide has been shown to be safe in reasonable injection volumes. Its low viscosity relative to standard contrast media makes it ideal for use with small catheters (3fr or smaller), and it is much less expensive than standard radiographic contrast material.

Since no injection system which controllably handles a compressible gas is produced for the angiographic market, we have undertaken the design and construction of prototypes of units for this application. No engineering data were available on flow rates and required volumes of carbon dioxide in catheters for angiographic applications. Phase I was targeted at obtaining that information. Actual carbon dioxide flow measurements were made on catheters under conditions similar to those found during clinical use. Dog studies were performed to determine best rates and volumes for imaging. A simple analytical flow model was also developed to permit prediction of general injector operation during development phases. The first prototype designed from these data will soon be ready for trials in a clinical setting.

Robert J. Hirko, Ph.D., Principal Investigator
Richard E. Sowls, Ph.D., Collaborating Investigator
Irvin F. Hawkins, M.D., Collaborating Investigator

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INDUSTRIAL & BIOMEDICAL SENSORS CORPORATION
Diastolic Pressure Determination by Phase Discrimination
GRANT NUMBER: 2 R44 HL 31895-02

Recent recognition of the health hazard associated with severe and mild hypertension has prompted clinicians to consider drug therapy even in cases involving only moderately elevated diastolic pressure. Consequently, an accurate determination of the diastolic pressure becomes increasingly important and desirable. Although diastolic pressure is a uniquely defined parameter, there is a great uncertainty with regard to its determination when a conventional sphygmomanometer is used. We undertook a study of a technique based on phase discrimination which would allow determination of the diastolic pressure without the dilemma of choosing between Phase IV, Phase V, and other criteria. When a Riva-Rocci cuff is inflated, a time lag exists between the arrival of the arterial upstroke and the generation of Korotkoff vibration. This time lag decreases steadily as the cuff pressure is lowered, and it diminishes as the cuff pressure approaches the true diastolic pressure. The diminution of this time lag is easily detectable electronically, and it can be a more objective, reliable, and accurate criterium for diastolic pressure indexing. The diastolic data yielded by time measurements or phase discrimination had been found to correlate with those obtained by manual auscultation (correlation coefficient, 0.89 and standard deviation 7.14 mmHg).

Because the diastolic pressure measurements obtained through manual auscultation are subject to the uncertainty of Phase IV/Phase V dilemma, the phase discrimination technique can be positively validated only by direct comparison with invasive pressure readings via indwelling catheters. Results of a study involving patients undergoing clinical cardiac catheterization will be presented. The central aortic pressure will be compared with the indirect diastolic pressure obtained by phase discrimination.

Kuo-Wei Chang, Ph.D., Principal Investigator
Herbert B. Hechtman, M.D., Collaborating Investigator

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LAWRENCE MEDICAL SYSTEMS
Continuous Monitoring of Doppler Cardiac Output
GRANT NUMBER: 2 R44 HL 31920-02

The ability to determine cardiac output (CO) during surgery aides in assessing the etiology of hypotension and the adequacy of myocardial function. The intravascular catheter thermodilution method of measuring CO is the most frequently used approach but provides only intermittent values, and there are a number of complications associated with its use. Doppler ultrasound offers a means of measuring CO both relatively noninvasively and continuously. The hypothesis of this study is that it will be possible to determine changes in cardiac output by monitoring descending thoracic aortic blood velocity using a Doppler probe placed in the esophagus and the descending aortic blood velocity, once calibrated against CO, will provide a means of continuously monitoring cardiac output intraoperatively.

The study population consists of patients undergoing elective surgery under general anesthesia requiring hemodynamic monitoring by means of a pulmonary artery catheter. Descending aortic velocity is measured using a transesophageal Doppler probe. The transesophageal Doppler probe consists of a 6 millimeter split piezoelectric disc (2.5 MHz) mounted on the tip of an esophageal stethoscope. The Doppler instrument is a continuous-wave ultrasound Doppler instrument developed by Lawrence Medical Systems.

In a feasibility study, changes in cardiac output as measured by thermodilution were compared with changes in descending aortic blood velocity. The correlation coefficient or r value was 0.84. The slope of the regression line was 1.09 and the Y intercept was -0.08. Following refinements of the transesophageal Doppler probe, the Doppler instrument, and application techniques resulted in initial findings in a multisite study of correlation coefficients from 0.87 to 0.89.

Our results to date show that measurements of descending aortic velocity have a relatively high degree of correlation with cardiac output as measured by the thermodilution technique and that good ultrasonic Doppler signals can be obtained in humans from a probe placed in the esophagus during general anesthesia.

Steven R. Barnes, BSEE, Principal Investigator
Paul H. Jones, Ph.D., Clinical Affairs Coordinator

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UNIVERSITY OF UTAH
Tomographic Digital Subtraction Angiography
GRANT NUMBER: 5 R01 HL 31984-02

Conventional circular tomography has been combined with DSA (digital subtraction angiography) in an attempt to improve DSA image quality. Our experience to date indicates that both artifact due to motion and confusion due to vessel overlap are substantially mitigated with this imaging approach. Currently, a patient study is under way to assess the potential of tomographic DSA with non-selective aortic arch injections for the diagnosis of head and neck vascular disease.

The imaging protocol we use predominately is to acquire pulsed radiographic images at a rate of 5.33 images per second during continuous circular tomographic motion (20°). A total of 48 images are digitized from an II-TV system attached to the Exatome^{R} tomography unit during three consecutive periods of tomographic motion. With the rotation speed set at 3 seconds per period, images are acquired for a total of 9 seconds. Following acquisition of the 16th image, 30-45 ml of 43 percent contrast material are power injected into the aortic arch via a 5 french pigtail catheter at a rate of 10-15 ml/sec. Sixteen subtraction projections are formed at each of the 16 projection angles. These 16 DSA images images then are used for tomosynthetic reconstruction. Eight to 16 planes are synthesized at a spacing of 0.4-0.6 cm apart, spanning the vascular anatomy of interest.

Display of the 3-D vascular tree from tomosynthesized "slice" images has proved to be problematic. As an alternative to displaying a series of tomosynthetic slices, an alternate display strategy has shown great promise. Once the 16 subtraction pairs have been formed, rather than tomosynthesize slice by slice, the images are presented in a movie loop played at approximately 16 frames/sec. This display gives the appearance of a vascular tree precessing at about 1 rev/sec. The presented display gives a true sensation of three-dimensionality. Widening the geometry to a tomographic angle of 40° also improves the three-dimensionality of the display. Interactive graphics that will allow us to identify vascular structures in three dimensions are being developed as well. Cardiac applications also are being explored.

Our work to develop a circular tomography device that can acquire tomograms in as little as 0.010 seconds is continuing. Current status of the rotating x-ray source and the image intensifier displacement circuitry will be reported.

Robert A. Kruger, Ph.D., Principal Investigator
James A. Sorenson, Ph.D., Collaborating Investigator
James A. Nelson, M.D., Collaborating Investigator

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ARZCO MEDICAL ELECTRONICS, INC.
Swallowable Electrodes for Temporary Cardiac Pacing
GRANT NUMBER: 2 R44 HL 32378-02

For certain electrophysiologic studies, transesophageal atrial pacing offers an alternative to transvenous catheterization and, with the development of an easily swallowed pill electrode, becomes a simple and noninvasive clinical procedure. During the past year, we have designed a stimulator for transesophageal atrial pacing for the diagnosis of conduction disorders and differentiation of automaticity. This new stimulator is microprocessor-based and programmable.

When completed, the Arzco Programmable Stimulator Model 8 will have three modes of operation:

1. Continuous Stimulation: Constant rate pacing at a preset cycle length.

2. Asynchronous Extrastimulation: Delivery of extrastimuli at preset coupling intervals following n paced beats at preset cycle length.

3. Synchronous Extrastimulation: Delivery of extrastimuli at preset coupling intervals following n sensed or tachycardia beats.

The operator enters the S1 rate, S2 through S4 intervals, and the number of S1's (either paced or the patient's sensed rhythm). Depending on the mode in which the instrument is operating, the device is designed to deliver a continuous train of pulses at a rate selected by S1 (Mode 1), deliver a specified number of S1's followed by S2 through S4 pulses (Mode 2), or sense a specified number of the patient's beats followed by S2 through S4. Following parameter entry by the operator, the working part of the program, written in Intel 8080 assembly code, is called. This program initializes counters 1 to 5 to count out the interval determined by the S1 rate, the S2 through S4 intervals, and the pulse duration, respectively. The final design has been successfully implemented on a logic development system.

Charles E. Yurkonis, M.D., Principal Investigator
Janice M. Jenkins, Ph.D., Co-Investigator
Robert Arzbaecher, Ph.D., Co-Investigator

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UNIVERSITY OF WISCONSIN, MADISON
Quantitation of Myocardial Blood Flow and Perfusion
GRANT NUMBER: 5 RO1 HL 32742-02

Although the measurement of mean arterial flow in coronary and peripheral vessels has been reported using radiographic techniques, many of the errors involved in these measurements have been ignored. We have devised techniques to: (1) Correct for magnification and vessel foreshortening, (2) check for pixel size variation across the face of the imaging tube, and (3) ensure uniform mixing of contrast material during intracoronary injections by using a special catheter. In addition, we are testing a new technique to measure pulsatile flow rather than mean flow in peripheral vessels.

We have used an 8 cm stainless steel bar and an angiographic balloon catheter with radiopaque rings 2 cm apart to correct for magnification in coronary artery flow studies. The correction for magnification provided measurements of 4.76 and 4.81 pixels/mm respectively, showing good consistancy between techniques. By imaging a wire grid of known proportions, we found that geometric distortion in our region of interest was only 2 percent at the edge when compared to the center of the field. Although this difference does not represent a significant distortion, it should be checked prior to performing any quantitative studies. By measuring the length of the coronary artery between two diagonal branches in PA and lateral projections (two projections 90^{o} apart), we were able to correct for foreshortening using the formula $L^2=L_x^2+L_y^2+L_z^2$, where L is the true length and L_x, L_y, and L_z are the projections along the three orthogonal axes. The apparent length can be calculated by the formula $L_a^2=L_x^2+L_y^2$. The actual length can be found by combining the above formulas ($L^2=L_a^2+L_z^2$) and measuring L_z from one of the two projections. We tested this method by suturing a 5.2 cm flexible wire along the course of the coronary artery and imaging the dog in the PA and lateral projections. Using these calculations, we obtained length determination of 5.13 cm and 5.19 cm. We also designed a catheter with four 0.1 mm side holes that provided excellent mixing within 1 cm of its tip.

A 75 percent reduction in arterial diameter is necessary before a reduction in mean flow is observed. However, lesser obstructions may produce changes in the pulsatile flow pattern. Using a computer analysis of the concentration gradient of iodine between the distal and proximal portions of an artery, we have constructed pulsatile flow patterns in dog femoral arteries following injection of contrast material in the abdominal aorta. Instantaneous flow velocities were determined at a rate of 60 points/sec angiographically and compared to continuous recordings from an electromagnetic flowmeter. Over a range of -100 to +600 cc/min, the correlation between the two techniques was excellent (R=0.96, MSE=24 ml/min). We anticipate applying this technique to measurements of coronary artery flow. Using these methods, accurate, reproducible measurements of both mean and pulsatile flow in peripheral and coronary artery vessels may be possible.

P. David Myerowitz, M.D., Principal Investigator
David K. Swanson, Ph.D., Co-Principal Investigator
George G. Rowe, M.D., Co-Investigator
Kim M. Watson, B.S., Co-Investigator

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McCORMICK LABORATORIES, INC.
Development of Pediatric Catheters That Reduce X-Ray Use
GRANT NUMBER: 1 R43 HL 33016-01

In pediatric anesthesia and intensive care, it is current practice to use tracheal tubes to ensure that a patent airway is maintained in the patient. The proper position of these tubes during use in infants is of critical importance, and x-rays are often obtained to determine the location of the distal tip of the tube relative to the carina and vocal cords. This procedure is undesirable because it does not provide a real time indication of position, and it exposes the patient to the usual hazards of radiation.

The objective of the company's product research program is to develop new types of pediatric catheters and simple, portable instruments as a system so that the anatomical position of the catheters can be determined directly and in real time by a noninvasive, magnetic sensing technique. The company has successfully demonstrated in cadaver studies that the new product can be utilized in a practical manner to determine the position of pediatric tracheal tubes. Furthermore, production prototype versions of the tube have been fabricated by economic, commercial processes that are capable of yielding disposable catheters of the highest quality. A production prototype version of the instrument has also been built in precommercial quantities, and final specifications for this noninvasive device will be established in conjunction with the completion of the planned preclinical studies.

The characteristics and operation of the catheter and instrument system will be described. Illustrative examples of comparative radiographic studies in cadavers will be presented.

William McCormick, Ph.D., Principal Investigator

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OPTICAL TECHNOLOGIES, INC.
Fiberoptic Continuous Flow Measurement Catheter
GRANT NUMBER: 1 R43 HL 33040-01

An optical fiber continuous flow measurement catheter capable of continuously measuring cardiac output was demonstrated. The experiments were performed using the Cardiac Pulse Duplicator of the Division of Mechanical and Material Sciences, Federal Drug Administration, Rockville, Maryland. Measurements were made in both a 1 cm and a 2.5 cm inside diameter tube. Flow rates were varied from 0.36 l/min to 1.12 l/min in the former case and 1.03 l/min to 6.25 l/min in the latter case. Simultaneous flow measurements were made with an electromagnetic Flow Meter, manufactured by Carolina Medical Sciences. Three methods were used to produce a differential pressure and thereby calculate flow. As is generally the case when using differential pressure to measure flow, a discrepancy occurs between the actual flow and that calculated from the measured differential pressure. The ratio of the actual flow to the calculated flow is called the discharge coefficient, C. The cause of the discrepancy is the turbulence produced by the measurement device. For all three methods, the respective values of C were essentially independent of the rate of flow. However, in two cases, the values of C were strongly dependent on the ratio of the probe diameter to the tube diameter. The value of C for the third case was only weakly dependent on that ratio.

Future investigations will concentrate on refining the probe design to one that exhibits predictable behavior with respect to the discharge coefficient (C) and that can be easily manufactured.

Charles M. Davis, Principal Investigator

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ELECTRONIC DESIGN & RESEARCH, INC.
Development of High Compression Ratio, Low Distortion
Analog Signal Processor
GRANT NUMBER: 1 R43 HL 33059-01

The major significance of this research effort was the development of the Time-Variant Data Processor (TVDP) as a hardware/software combination. Experimental results showed that its high compression ratio and low average distortion make it far superior to existing systems. The better result was achieved by combining the two methods to reduce a data stream. In the first step, the data reduction procedure employs a time of nonredundant sample codes (THRS) technique; in step two, this reduced stream of data undergoes further reduction by a technique similar to "null" or "blank" suppression, which eliminates a sample of equal time-interval (rate) by coding a number of them in a single byte. The second step was accomplished by the use of a very efficient software program. A Data Retriever was devised completely as a hardware. The TVDR technique was developed and tested for an input signal in the frequency range of DC to 23,000 Hz. It requires only 22 words (on the average) to store a high-quality ECG complex and 50 words to store a Paced Rhythm with a .1 percent distortion. For a lower level of accuracy, the number of words required for storage was decreased. The reduction of the number of words makes it possible to send high-quality multiplexed signals through the telephone line (or any other communication channel).

Based on the TVDC technology, EDR is developing a Universal Hybrid Module (UHM) for analog data storing/transmitting at a wide frequency range. The first commercial application for it is in an Intelligent Holter Recorder (IHR). The UHM will give to the end-user the options of storing information in a replaceable memory module and/or sending information via a telephone line and/or playing back (sending information previously stored in the memory). The IHR is a "smart," low cost, portable device with a large memory capacity (one megabyte). Maintenance free, low power consumption, and immediate readiness will make it an important addition in obtaining vital information for preventive medicine. The sophisticated software recognizes and stores abnormal beats and/or heart rates and/or arrythmias with a high sensitivity. A low False Positive rate will make the memory (which could store up to 5,200 beats) last more than 48 hours.

Vladimir A. Shvartsman, Ph.D., Principal Investigator

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UNIVERSITY OF PENNSYLVANIA
NMR Measurement of Blood Flow in the Cat Carotid
GRANT NUMBER: 1 R01 HL 33236-01

Magnetic resonance imaging (MRI) of blood vessels shows a variety of different effects due to blood flow, depending on the particular imaging technique employed. Many modified MRI techniques have been proposed to employ these effects for the noninvasive measurement of blood flow, but there has been little study of their accuracy and usefulness. This project seeks to evaluate three major classes of MRI flow measurement techniques, saturated spin time-of-flight, excited spin time-of-flight, and velocity-dependent phase shifts, both in vitro and in vivo.

A 1.4T experimental MRI instrument is being programmed to explore different flow effects in MRI and to implement specific flow measurement techniques. A selective saturation time-of-flight technique is currently being implemented which includes compensation for phase shifts due to motion along imaging gradients and has provision for cardiac gating. It is being tested in vitro with controlled flows through tubing in a phantom model. An in vivo model using an implantable ultrasonic flow transducer that is being modified by the manufacturer (Transsonics) for use in the MR imager is being developed with placement of the flow probe around the distal aorta of the New Zealand white rabbit (3-4 kg). An interface for computer data acquisition from the flow probe is being built to permit direct comparison of MRI and ultrasonic flow measurements.

The baseline MR imaging technique with phase compensation is working well; the selective saturation feature is being tested. The in vitro model has stable, continuous flows controllable to over 75 cm/sec average velocity through 0.625 cm i.d. tubing. The flow probe implantation technique is developing well with 2 week implantations being well tolerated without vascular compromise, as evaluated by angiography.

Although the methodology is still being developed, good progress is being made toward a system which will permit ready implementation and both in vitro and in vivo testing of a variety of MRI flow measurement techniques. This will provide an objective means of evaluation of the potentially very useful noninvasive techniques of measurement of blood flow with MRI.

Leon Axel, Ph.D., M.D., Principal Investigator
John Leigh, Ph.D., Collaborating Investigator
Peter Joseph, Ph.D., Collaborating Investigator
Martin Reivich, M.D., Collaborating Investigator
Jeffrey Wortman, D.V.M., Collaborating Investigator

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DUKE UNIVERSITY
Signal Acquisition and Analysis in Cardiac Mapping
GRANT NUMBER: 5 R01 HL 33637-01

Mapping the sequence in which the myocardium is electrically activated during normal and abnormal cardiac rhythms has been shown to be useful in the surgical treatment of arrhythmias unresponsive to medical therapy and in the understanding of the mechanisms of those arrhythmias through basic and clinical investigations. The identification of arrhythmogenic regions by mapping can reduce the amount of tissue to be resected during surgical procedures. Detailed mapping of experimental and clinical arrhythmias can be useful in elucidating the underlying principles in the onset and maintenance of life-threatening rhythm abnormalities.

Technical problems associated with adequate mapping techniques include the high data rates involved, the need for fast turnaround of results and difficulty in conveying the complex results to the experimenter or clinician. Because the arrhythmias of interest change from beat to beat, or because they are short-lived, it is necessary to acquire data from many electrodes simultaneously, sampling each signal at a rate of at least one kilohertz, so that overall rates for useful systems are at least 250,000 bytes per second. The user of the system needs results produced rapidly, so that appropriate surgical maneuvers or experimental interventions can be carried out. The need for high speed in data acquisition and analysis is complicated by the fact that the understanding of the physiology is incomplete, requiring flexibility to be maintained in the system design. Finally, it is necessary to be able to present graphical results to the user rapidly and effectively.

We have developed a mapping system that addresses these problems. The system is capable of an overall data rate of 128,000 data samples per second (256,000 bytes per second). The data are digitized, recorded continuously for up to an hour on a video cassette and displayed in analog form in real time on suitable recorders. The analog front end parameters, including gains, filter cutoffs, and analog displays, are controlled by a microcomputer. The data can be simultaneously input to a dual-ported memory, acting as a circular or one-shot buffer. When desired, the data are transferred to the host computer for analysis. The electrograms are processed, and local activations are detected and timed automatically, with possible editing by the operator. Finally, the results are presented in several graphical forms, including isochronous maps.

This system has been used in basic and clinical research by investigators with a variety of technical backgrounds, proving to be effective in both situations. The system software has been changed often to incorporate new knowledge and hypotheses. Development is continuing to improve the speed and effectiveness of the hardware and software.

William M. Smith, Ph.D. Principal Investigator
Raymond E. Ideker, M.D., Ph.D., Collaborating Investigator
Seth J. Worley, M.D., Collaborating Investigator

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DESERET RESEARCH COMPANY--UBTL, INC., DIVISION
Myocardial Recovery After Acute Ischemic Heart Failure
GRANT NUMBER: 1 RO1 HL 33805-01

A dysfunctional heart may recover if mechanical "rest" is provided. Utilizing biventricular bypass or cardiopulmonary bypass, a variety of methods to produce heart failure have been evaluated, including prolonged normothermic ventricular fibrillation-defibrillation, aortic cross clamp (ischemic contracture model), and recently repeated short periods of aortic occlusion-reperfusion. Our goal is to produce a maximally dysfunctional heart with minimal necrosis and study myocardial recovery. Left atrial to aortic bypass produces excellent hemodynamics with bypass flows in the range of 6-7 L/min with normal LAP, RAP, PAP, and AoP but an undecompressed LV (LVP = AoP). In contrast, LV apical to aortic bypass produces a decompressed LV but elevated LAP, PAP, a right ventricular bypass shunt because of an incompetent pulmonary valve with resultant ventricular septal shift to the left, decreased LV apical blood withdrawal and bypass flow (3-4.5 L/min). The greatest amount of subendocardial necrosis (30 percent) rapidly occurs during LA to aortic bypass because of the elevated LVP during ventricular fibrillation. Combined LA and LV blood withdrawal (with a small LV sump) produces excellent hemodynammics, a decompressed LV with minimal subendocardial necrosis (5-10 percent) but markedly impaired LV function (LAP > 25 mmHg, AoP = 50 mmHg). The importance of this type of heart failure is a model to evaluate pathologic and biochemical changes (e.g., high energy phosphates and mitochondrial function), and mechanical and pharmacologic therapies during myocardial failure and the transition to recovery.

Jeffrey L. Peters, Ph.D., M.D., Principal Investigator
Clifford S. Kwan-Gett, M.D., Co-Principal Investigator
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James T. Wu, Ph.D., Biochemist
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UNIVERSITY OF ALABAMA AT BIRMINGHAM
Three-Dimensional Reconstruction of 2-D Echocardiographic Images
GRANT NUMBER: 1 RO1 HL 33839-01

To minimize processing time in 3-D reconstruction, three algorithms were applied to 26 2-D echo images of circular holes of known diameters (.8 - 2.75 cm) drilled in static objects. The aim was to assess their accuracy for use in computer automated edge detection. The digitized video taped images were planimetered and processed, algorithms: (A) a simple contrast stretch of input images, (B) smoothing the digitized images by replacing each point with the average of itself and its nearest neighbors followed by taking a radial first derivative, and (C) a combination of A and B and replacing images with the value of radial first derivative. All areas were computed in a blinded fashion and compared with known values:

	r	REcm^2	RMS
A	.98	.22	.25
B	.99	.16	.24
C	.99	.21	.33

RE = residual error, RMS = root mean square

Also, comparable results were obtained from all three different sampling groups (phantom, human liver tissue, foam rubber material) studied with each algorithm. All algorithms appear accurate and comparable, but in terms of implementation, algorithm B appears the easiest to use for automatic edge detection, hence may be ideal for accurate 3-D reconstruction of 2-D echo images.

Navin C. Nanda, M.D., Principal Investigator
Amitabha Ghosh, Ph.D., Co-Principal Investigator
John R. Schott, Ph.D., Co-Investigator

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PERINATRONICS MEDICAL SYSTEMS, INC.
Adaptive Cancellation in Electrocardiography
CONTRACT NUMBER: 1 R44 HL 34898-01

Only a few carefully controlled non-invasive observations have been made on the developing fetal myocardiogram. The goal of this research is to investigate non-invasive diagnostic instrumentation techniques to monitor the fetal electrocardiogram (ECG), fetal heart rate (FHR) and FHR variability.

Our approach is to assess the combination of digital signal processing techniques, called feedforward adaptive cancellation, using a 16-bit microcomputer to obtain a real time non-invasive instrumentation technique for continuous fetal ECG studies. In particular the aims of this research are to assess the speed and effectiveness of a real-time cancellation of the maternal ECG interference signal and background muscle noise to obtain a continuous record of the fetal ECG signal from maternal abdominal surface potential recordings. The development of this continuous fetal ECG record will thus enable us to measure short term FHR variability on an R to R interval basis.

The methodology is to initially optimize the effectiveness of our feedforward adaptive signal processing to cancel the strong maternal abdominal ECG interference and implement the algorithms to provide efffective and potential real-time cancellation yielding an extraction of the fetal ECG record. We will configure a 16-bit microprocessor system with programmable read only memory (PROM) firmware to provide real-time operation to assess the performance, in terms of both speed and effectiveness, of the adaptive system to present a continuous fetal ECG and FHR variability record. Finally, we will enhance our adaptive algorithms to also cancel high electromyographic noise levels to extend performance. The raw fetal ECG data per se is obtained non-invasively from an array of standard ECG electrodes placed on the maternal abdomen during the antepartum period. This data is first amplified and then stored on computer disk media for subsequent processing.

Our preliminary results suggest that the adaptive algorithms are effective in maternal ECG cancellation to achieve cancellation in excess of 25 dB (i.e., one part in 18) to provide cancellation to the level of approximately 5 microvolts. This can be compared with a typical 15 to 20 microvolt fetal R-wave measured at the maternal abdomen. Preliminary evaluation of real-time processing has been obtained from the execution speed of portions of the algorithms executed on the Digital Equipment Corp. LSI-11 processor with the KEV-11 extended instruction set.

This research will lead to a continuous extraction of the weak fetal ECG signal from maternal abdominal surface potential measurements. Improvements in non-invasive fetal ECG instrumentation methodology for use on the prenatal fetus will enable us to assess fetal myocardial development throughout gestation.

Thomas H. Frank, Ph.D., Principal Investigator
Otis R. Blaumanis, Ph.D., Research Associate

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STANFORD UNIVERSITY
Plaque Characterization Using Magnetic Resonance
GRANT NUMBER: 1 R01 HL 34962-01

We propose the use of magnetic resonance to characterize plaques. The multivariable nature of NMR is particularly suited to this problem. For adequate characterization, we require a system of localization and a method for studying the signal from each voxel. For localization, we will study a system of time-varying gradients which enables rapid, high-resolution imaging limited only by SNR. In addition, using time-varying gradients, the spectroscopic information remains intact. Information from both the hydrogen and phosphorus spectra will provide significant characterization information relating to lipids, metabolic activity, etc. The basic imaging properties, using the strong water line, will provide high resolution information on the geometry and texture of the plaque. Relaxation times will provide additional characterization information. Relatively solid calcified regions will have very short T_2 relaxation times and can be identified in that manner.

Weak spectroscopic components from relatively small voxels provide relatively low values of SNR. However, we can make use of estimation theory, using the wealth of a priori information, to provide a reasonably accurate estimate. Each frequency is known beforehand so that we can use this information to estimate the unknown amplitude.

Magnetic resonance is totally noninvasive and nontoxic and has no penetration problems with deep-lying vessels. It is therefore a very appropriate choice for plaque characterization.

Albert Macovski, Ph.D., Principal Investigator

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Biomaterials, Rheology, and Thrombosis

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ABIOMED
Primary Reference Materials: Low Density Polyethylene (LDPE)
CONTRACT NUMBER: NO1-HV-92932

During tne period between September 30, 1982, and the present date, quantities of stable, reproducible, and chemically pure LDPE were prepared, characterized, packaged, sterilized, and supplied to qualified investigators under this contract. Quality-assurance tests are performed periodically to insure constancy of physiochemical properties.

ABIOMED has kept the LDPE Primary Reference Materials continuously stored under controlled conditions in its clean room facility and will continue to make samples available to interested investigators. The samples are available in sheet and tube form. The sheets have nominal dimensions of 2.54 cm x 7.62 cm x 0.025 cm and the tubes are available in 0.5, 1.0, or 1.5 meter lengths with nominal internal diameter of 0.41 cm and outside diameter of 0.49 cm.

Detailed characterization data are available to investigators interested in using these materials. To facilitate their procurement, a brief program overview and request form are included in the appendix. The completed forms should be mailed directly to the NHLBI/DTB Program Office to the address indicated on the forms.

Stephen C. Vaughan, Project Manager
David M. Lederman, Principal Investigator

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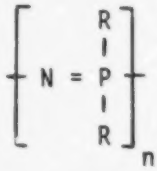
PENNSYLVANIA STATE UNIVERSITY
Poly(organophosphazenes) for Biomedical Uses
GRANT NUMBER: 5 RO1 HL 11418-15

New biostable polymers are needed for the construction of a wide range of biomedical devices, such as heart pumps, blood vessel prostheses, artificial kidneys and lungs. In addition, new bioactive polymers are required for a number of applications that range from anticoagulent materials, controlled release of chemotherapeutic agents, and enzyme- or cell-immobilization systems.

We have developed a new class of polymers that have many advantages for use in all these areas. These polymers are polyphosphazenes, of structure I.



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The key advantage of these polymers for biomedical applications is that they are prepared by a substitutive process in which the organic side group, R, is introduced after the polymer chain has been assembled. Thus, a very broad range of organic side groups can be incorporated into these systems, with the properties of the final polymer being dependent on the nature of the side group.

Recent work has shown that a series of hydrophilic, membrane-forming polymers can be prepared with the use of alkoxy ether and alkylamino side groups. Some of these materials, when treated with lithium triflate, have proved to be excellent solid electrolytes for lightweight rechargable battery applications. Others are being investigated as semipermeable membranes. The blood compatibility of amphiphilic polymers with hydrophobic (CF_3CH_2O-) and hydrophilic ($CH_3OCH_2CH_2O$-) side groups has also been investigated. The greater the hydrophobicity, the lower the tendency for blood coagulation.

In addition, a series of polyphosphazenes with both aryloxy- and amino acid ester side groups have shown promise as erodable substrates for the controlled release of chemotherapeutic agents. This work has been done in collaboration with Dr. R. Langer's group at MIT.

Progress has also been made in the use of polyphosphazenes as substrates for the immobilization of enzymes such as trypsin and glucose-6-phosphate dehydrogenase, with retention of the enzymic activity and stabilization of the enzyme against denaturation. These are considered to be prototype systems for artificial organ development.

Harry R. Allcock, Ph.D., Principal Investigator

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WASHINGTON UNIVERSITY
Erythrocyte Deformability and Vascular Pathophysiology
GRANT NUMBER: 5 R01 HL 12839-16

Erythocyte deformability is an important factor in microvascular function and is being widely investigated under both static and dynamic conditions. The overall objective of this project is to extend current knowledge of the deformability of normal and pathologic erythrocytes with emphasis on those properties which govern the individual cell's capacity to change shape in response to rapidly varying flow conditions. Of particular interest are the physical/chemical changes in erythrocytes which may result in their sequestration in the spleen and other organs in vivo.

The experimental approach is to subject age-fractionated populations of erythrocytes to well defined shear flows in the rheoscope, a viscometric device consisting of counter-rotating cone and plate. The steady state motion and deformation of cells subjected to shear flow and also their transient shape recovery following abrupt flow cessation are recorded photographically and on videotape. Measurements of steady-state elongation, membrane rotation rate (i.e., tank-treading frequency) and characteristic length-recovery time are used in conjunction with simplified mathematical models to determine elastic and viscous moduli of the erythrocyte membrane and cytoplasm. Simultaneous physical and chemical assays are also performed in a search for correlates of impaired deformability.

Current studies are focused on (1) erythrocytes from hypercholesteremic rabbits, (2) erythrocytes from humans on diets high in carbohydrates and/or cholesterol, (3) erythrocytes parasitized by different strains of malaria (plasmodium berghei, babesia microti), (4) the effects of certain pharmaceutical agents on erythrocyte deformability. Attempts are also being made to determine in vivo sequestration in the spleen and other organs of the rat as a means of verifying physiologic significance of in vitro indications of impaired deformability.

S. P. Sutera, Ph.D., Principal Investigator
D. J. Krogstad, M.D., Collaborating Investigator
J. R. Williamson, M.D., Collaborating Investigator
G. I. Zahalak, Ph.D., Collaborating Investigator

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RICE UNIVERSITY
Flow Effects on Leukocyte Function and Surface Adhesion
GRANT NUMBER: 5 R01 HL 17437-09

The objectives of this research project remain to quantify the effects of mechanical forces on leukocytes and to examine biochemical mechanisms for these functional alterations as well as leukocyte adhesion to surfaces coated with purified proteins and endothelial or smooth muscle cells.

The development of delayed coagulation abnormalities after surgery is a significant clinical problem. One possible cause is expression of monocyte tissue factor activity (TFA), stimulated by mechanical trauma or artificial surface interaction. In this study, leukocytes and separated leukocyte fractions were exposed to controlled mechanical trauma in vitro, which in turn caused TFA generation in certain of the sheared samples. The presence of lymphocytes appeared to be necessary for the direct shear stress induced expression of TFA. However, all sheared cells retained their viability and ability to produce TFA, because if stimulated with endotoxin, significant TFA was assayed.

The effect of shear stresses on human lymphocyte function including proliferative responses to phytohemagglutinin-P, interleukin-2 (IL-2) synthesis, cell viability, cell enlargement and cell density was studied. Shear stress levels investigated were similar to those found in blood pumps and dialysis units. At 100 and 200 dynes/cm^2 for 10 minutes, a portion of the mononuclear cell suspension was lethally damaged. Shear stressed cells when cultured at 1×10^6 cells/ml did not incorporate significant amounts of thymidine nor synthesize detectable levels of IL-2. When the shear stressed cells were cultured at cell densities of 0.5×10^6 cells/ml and 0.25×10^6 cells/ml, they incorporated significantly greater amounts of thymidine along with concomitant increase in synthesis of IL-2. The data suggest that a fraction of cells were shear damaged and that such damage inhibited the proliferation of the other cells in a density dependent manner.

To study leukocyte interactions with cultured endothelial cells or specific proteins, epifluorescent videomicroscopy is being used. The endothelial cells are cultured on slides which constitute one side of a flow chamber, and can be exposed to the leukocytes in a constant head flow loop, or with a single pass syringe pump system. Events are recorded on videotape using a Hamamatsu Silicon Intensifed Target (SIT) camera. This allows low level UV excitation and minimum leukocyte functional alterations. Quantitation is done with a Perceptive Systems Digital Image Processor. In order to visualize leukocyte-vessel wall interactions in whole blood, the leukocytes are labelled with quinacrine dihydrochloride.

Larry V. McIntire, Ph.D., Principal Investigator
Suzanne G. Eskin, Ph.D., Collaborating Investigator
Robert Rich, Ph.D., Collaborating Investigator

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UNIVERSITY OF UTAH
Initial Events in Thrombus Formation on Surfaces
GRANT NUMBER: 2 R01 HL 17623-11

Research efforts in this laboratory are presently investigating interactions of synthesized heterogeneous hydrophilic/hydrophobic multiblock copolymers and triblock copolymer-heparin surfaces with whole blood, plasma, and platelets. Transmission electron microscopy has shown these surfaces to have microphase separated structure that has been suggested to control protein adsorption and platelet adhesion. Multiblock copolymers of polyethylene oxide (PEO) and polystyrene (PSt) have been synthesized and are unique in that they can be altered on a molecular scale to change bulk composition surface energy, hydrophilic/hydrophobic character, and surface morphology--all parameters involved in antithrombogenicity. The block copolymers of pharmacologically active heparin covalently linked to PEO and PSt have been synthesized and show significant bioactivity in in vitro assays with rabbit plasma over nonheparinized controls. Protein adsorption/desorption studies using columns of copolymer-coated beads indicate that multiblock copolymer surfaces adsorb less albumin than homopolymer or glass surfaces and that this adsorbed layer is more stable. Adsorption and desorption kinetics are a function of copolymer hydrophilic/hydrophobic composition. Wilhelmy-Plate dynamic contact angle analysis demonstrates unique surface energies and mobilities associated with the copolymers. Hysteresis and contact angles, hence wettability, change with changes in copolymer composition. Hydration causes these changes to be more dramatic compared to homopolymer surfaces. Platelet studies involving copolymer-coated bead columns are being evaluated to assess the affects of microphase-separated structure on binding and activation of platelets.

Sung Wan Kim, Ph.D., Principal Investigator
Teruo Okano, Ph.D., Co-Investigator
Jan Feijen, Ph.D., Co-Investigator
David Grainger, Research Assistant

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RICE UNIVERSITY
Studies on Mechanisms of Shear-Induced Platelet Activation
GRANT NUMBER: 5 R01 HL 18584-09

The importance of the shear field in promoting platelet-surface and platelet-platelet reactions is known. Studies have been carried out in rotational viscometers in which carefully controlled, uniform shear fields are used to gain insight into the pathways of shear-induced activation in the absence of added agonists.

Bernard-Soulier (B-S) platelets were found to not aggregate in the shear field under conditions where there would be pronounced aggregation of normal platelets. Platelets were incubated with a monoclonal antibody which blocks vWF binding. The antibody was found to strongly inhibit shear-induced aggregation. These data indicate that GPIb plays a significant role in platelet aggregation under conditions of moderate or high shearing stress, and suggests the possibility that moderate or high shear forces may serve as an in vivo analog of ristocetin as a cofactor in vWF binding.

Similar studies were carried out on the role of platelet GP IIb-IIIa in shear-induced aggregation. Platelets from a patient with Glanzmann's thrombasthenia did not aggregate in the shear field. Normal platelets incubated with an anti-GP IIb-IIIa monoclonal antibody (which blocks fibrinogen binding to platelets) were also found not to aggregate in the shear field. These results suggest that reversible platelet aggregation dependent on fibrinogen binding is a necessary prerequisite to shearinduced aggregation.

Quin2 was used to study the role of intracellular calcium ion concentration in mediating shear-induced platelet activation. Shear-induced aggregation was significantly suppressed by Quin2 treatment. Shear-induced dense granular release and cellular lysis were significantly increased by Quin2 treatment. These results suggest that intracellular calcium ion mobilization is an important, early step in shear-induced platelet activation. Additionally, Quin2 appears to have membrane effects resulting in increased platelet fragility. Thus, the findings raise questions on the suitability of Quin2 as an intracellular calcium ion probe in studies in shear fields.

Studies with another fluorescence intracellular calcium ion probe, Indo-1, show much promise. Work is proceeding to modify a rotational viscometer to permit continuous monitoring in the shear field of optical signals indicative of aggregation, release, and intracellular calcium ion concentration.

J. D. Hellums, Ph.D., Principal Investigator
D. M. Peterson, Ph.D., Collaborating Investigator

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UNIVERSITY OF WASHINGTON
Cell and Protein Reactions With Foreign Materials
GRANT NUMBER: 5 R01 HL 19419-09

The general hypothesis being tested in these studies is that the surface chemistry of the material dictates the organization of the adsorbed protein layer which forms upon exposure to the biological mileu, that this organization in turn dictates the subsequent response of the cells with the surface, and that the degree of "biocompatibility" of any material is a direct reflection of this mechanism. Specific cells (platelets, macrophages, and fibroblasts) and proteins for which these cells have receptors [fibrinogen and von Willebrands factor (VWF); immunoglobulin G and complement C3; and fibronectin, respectively] are being studied with series of polymers varying widely in their surface properties (HEMA-EMA; monomer gas/plasma discharge treated surfaces [(M/PD)]. The 3T3 cell-fibronectin studies support this hypothesis because 3T3 cell spreading is linearily correlated with fibronectin adsorption from serum on many surfaces. However, the adhesion of non-activated or ADP-activated baboon platelets to surfaces pretreated with varying dilutions of plasma does not correlate with the different amounts of adsorbed fibrinogen. In addition, the spreading of mouse peritoneal macrophages on HEMA-EMA surfaces or on glass pretreated with various dilutions of serum does not correlate with IgG adsorption. The platelet and macrophage results may indicate the adsorption of other proteins are more important to these cells. Alternatively, how the proteins are adsorbed may be more important than how much is adsorbed, e.g., the tightness of binding or how they are packed with co-adsorbed proteins may influence how attractive they are to the cells.

Several new, unexpected observations were also made: 1). Evidence for differences in the way proteins are adsorbed to surfaces was obtained from studies of the elutability of fibrinogen and albumin from polymers with SDS. Protein elutability from polymers decreased slowly over a period of days at 4°C, proceeded much more rapidly at elevated temperatures, while the rates and degree of decrease depended on polymer type. Proteins appear to be adsorbed to surfaces in a variety of ways ranging from weakly to very tightly held, at least partly due to differences in rates of transition to the final state. 2). The contact of washed 3T3 cells with protein free surfaces in protein free media often results in cell death (as measured by trypan blue uptake and inhibition of growth), but this strongly depends on the polymer type. These results were totally unexpected and no one has yet offered a satisfactory explanation. However, it may be significant to note that both of the NHLBI/DTB reference materials (silicone rubber and polyethylene) cause extensive cell death under these conditions. 3). Lastly, new types of M/PD surfaces with greatly elevated fibronectin adsorption from serum were prepared. The growth of 3T3 and muscle myoblast cells on the new surfaces is increased substantially in comparison to standard culture dishes. Should these new surface treatments prove to facilitate endolheleal cell growth as well, the findings may be very important, especially since the M/PD technique is very amenable to coating complex devices such as woven vascular grafts.

Thomas A. Horbett, Ph.D., Principal Investigator
Buddy D. Ratner, Ph.D., Investigator
Allan S. Hoffman, Sc.D., Investigator

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UNIVERSITY OF UTAH
Novel Approach to Nonthrombogenic Polymer Surfaces
GRANT NUMBER: 2 R01 HL 20251-09

Prostaglandin (PGE_1) releasing Biomer was coated onto the surfaces of polyurethane tubing. Short-term evaluations of these AV shunts implanted in rabbits indicated that platelet activation after adhesion was minimal. Although the PGE_1 released at the blood-material interface minimized platelet pseudopod formation, systemic effects of PGE_1 in circulating blood were not detected by platelet aggregation measurement.

Heparin-immobilized polyurethane catheters implanted in canine femoral and jugular veins for 2-hour periods exhibited significant reduction in thrombus formation. The catheters coated with dispersed heparin provided a significant improvement in antithrombogenicity.

A covalently bonded conjugate of heparin and PGE_1 was synthesized to reduce fibrin formation and platelet aggregation simultaneously. Bioactivity tests on the conjugates (APTT and platelet aggregation) confirmed that the conjugate was biologically active. Rabbit AV shunt experiments reveal that the heparin-PGE_1 conjugate coated polyurethane shunts demonstrate excellent antithrombogenicity.

Small diameter vascular grafts of Biomer (3 mm ID) coated on inner surfaces with bioactive agents are being evaluated in long-term studies using implants of the designed system in carotid and femoral arteries of dogs.

Sung Wan Kim, Ph.D., Principal Investigator
Teruo Okano, Ph.D., Co-Investigator
Ryukichi Seino, M.D., Investigator
Harvey Jacobs, Research Assistant
John Lin, Research Assistant

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BATTELLE COLUMBUS LABORATORIES
A Molecule Approach to Blood Materials Interactions
GRANT NUMBER: 5 R01 HL 24015-06

The objective of this study has been the development of a Fourier transform infrared-based method whereby the adsorption of blood proteins under physiological conditions onto various surfaces can be studied. The procedure developed utilizes a flow cell with a rectangular channel, the bottom of which is a germanium crystal, which can be coated with the polymer of interest. Solutions ranging from single proteins through plasma and blood can be used with this cell at physiological flow rates in order to study both the adsorption rate and the adsorbate composition from the beginning of the process. Information is obtained from infrared spectra obtained during the adsorption using the germanium crystal in the attenuated total reflection mode. The raw spectra obtained are the combined spectra of the adsorbate, the solute protein, and water within the field of the evanescent wave of the reflecting infrared beam (ca. 4000 A), and the polymer coating (if any) applied to the germanium surface. Methods have been developed whereby this composite spectrum can be resolved to yield spectra of the adsorbate as it is being formed. From these spectra the kinetics of adsorption can be obtained, and progress has been made in both the quantitative and qualitative analysis of the composition of the adsorbate competitively deposited from a solution of proteins.

Studies with single proteins have shown that the bulk of the adsorption occurs within the first few minutes and that the adsorption is essentially irreversible. Competitive adsorptions have been done using binary protein solutions in contact with such surfaces as Biomer and alkylated cellulose. In comparison with germanium, a greater affinity of albumin in relation to gamma globulin for the synthetic surfaces has been seen. These studies will be extended to other surfaces and more complex mixtures of proteins, e.g., plasma. Flow adsorption runs using blood or plasma have shown that in the very initial period (a few seconds), low molecular weight nonprotein components reach the surface before the proteins as the plasma or blood displaces the initial saline solution. These components are as yet not identified, but their presence shows that the first proteins reaching the surface are adsorbing from an environment different from that of proteins reaching the surface after the "boundary" layer is in equilibrium with the bulk protein solution. This changing environment during the very initial period of exposure of blood to a foreign surface has not previously been considered, and its importance is being investigated.

Robert I. Leininger, Ph.D., Principal Investigator
David J. Fink, Ph.D., Collaborating Investigator
Krishnan K. Chittur, Ph.D., Collaborating Investigator
Timothy B. Hutson, B.S., Collaborating Investigator

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NEW YORK STATE DEPARTMENT OF HEALTH
Blood-Materials Interactions: The "Bridge" Problem
GRANT NUMBER: 5 R01 HL 24017-07

The overall scientific objective is to improve understanding of interactions between constituents of blood and foreign surfaces under conditions of cardiovascular use. The eventual practical goal is to define the surface or interfacial properties required of truly blood compatible materials. From the effects of a wide variety of physical and chemical agents on platelet adhesion and retention from flowing normothermic native and anticoagulated whole blood in conventional and siliconed glass bead columns, we concluded previously that plasma fibrinogen is a bridging macromolecule and that expression of platelet fibrinogen receptors, but not extension of filopodia, is necessary for adhesion during the first few minutes of contact. Subsequent experiments have shown, consistent with expectation, that agents which are known to compete with or otherwise inhibit fibrinogen binding to stimulated platelets (EDTA, 5.4mM; colchicine, 6mM; PGE_1, 1μM; caffeine, 5μM; α-(D+)-glucosamine, 0.05M) also induce the release of adherent platelets into platelet-free plasma.

The importance of the composition of the initial foreign surface is illustrated by freshly annealed glass which, with the standard contact protocol, exhibits less than 1 percent of the adhesion of conventional or siliconed glass bead columns. Furthermore, platelets in the effluent of native whole blood flowing through "clean" glass columns are as effective as control platelets in maintaining vascular integrity in the isolated perfused kidney assay. The results to date of experiments with pre-exposure to platelet-free plasma and sequences of purified proteins support the view that the relative nonthrombogenicity of "clean" glass in these assays reflects a depression in the rate of adsorption of fibrinogen from plasma as compared to the other substrates.

W. J. Dodds, D.V.M., Principal Investigator
J. A. Bergeron, Ph.D., Co-Investigator

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UNIVERSITY OF TORONTO, DEPARTMENT OF CHEMICAL ENGINEERING
AND APPLIED CHEMISTRY
Heparinized Materials: Blood Interaction
GRANT NUMBER: 5 R01 HL 24020-06

We continue to examine the potential for long-term thromboresistance offered by biomaterials containing immobilized heparin and the interactions with blood components that may be relevant to the various hypothesized but never proven concerns regarding the use of heparin in long-term implants.

Previous experiments with ^{125}I-thrombin have shown that surface-bound heparin (as a heparin-polyvinyl alcohol hydrogen) does not become saturated with inactive complex since it is readily displaced from the surface by component(s) in plasma (Thromb. Haemost. 50, 873, 1983). Recent attention has been focused on the activity of the bound heparin after exposure to thrombin and antithrombin III. Chromogenic substrate has been used to compare the thrombin inactivation capacity of fresh heparin-PVA coated tubes with those which have been exposed 2-10 times to thrombin and antithrombin III. Both bound thrombin activity and residual solution phase activity have been monitored. Each time crude bovine thrombin and excess of antithrombin III were circulated through a heparin-PVA tube, there was an approximate 75-percent reduction in solution phase color yield, indicating that the heparin-PVA tube can repeatedly inactivate thrombin. No such reduction was seen with thrombin alone or with a PVA tube without heparin. Thus, the immobilized heparin appears to act catalytically and is not consumed by prior exposure to thrombin and antithrombin III.

Platelet interactions are our current concern. Little difference in platelet response has been observed in vitro, among heparin-PVA, PVA, or chondroitin sulfate-PVA in a number of assays: washed human platelet adhesion at low shear rate, bead column retention of canine platelets from PRP, ^{14}C-serotonin release from canine platelets (PRP) recirculated through loops of coated tubing. These results support our working hypothesis that surface-bound heparin has no significant direct effect on in vitro platelet adhesion or aggregation and that the interaction of heparin-PVA with platelets is dominated by the reactivity of the PVA substrate. In vivo, however, surface-bound heparin may have a beneficial effect on platelets through its effect on the inactivation of thrombin; this is being examined through measurement of platelet survival in a chronic canine AV shunt.

Michael V. Sefton, Sc.D., Principal Investigator
Mark W. C. Hatton, Ph.D., Co-Investigator
Walter Zingg, M.D., Co-Investigator

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UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS
Blood-Material Interactions: Adsorption of Fibronectin
GRANT NUMBER: 5 R01 HL 24221-06

In previous studies concerning fibronectin adsorption on material surfaces, we found significant differences in the adsorption pattern depending upon whether the surfaces were exposed to pure protein solutions or protein mixtures. When hydrophilic or hydrophobic surfaces were exposed to pure fibronectin solutions, fibronectin adsorption isotherms displayed a typical saturation pattern. When serum or plasma were tested, however, fibronectin adsorption on the surfaces occurred in a complex fashion with maximum adsorption on surfaces exposed to 0.1 percent to 1.0 percent (v/v) serum or plasma solutions and decreased adsorption at higher serum or plasma concentrations. Biochemical assays showed that the ability of fibroblasts to exhibit short-term attachment and spreading on the protein-treated surfaces correlated well with the fibronectin adsorption pattern.

During the present year, we have measured platelet attachment and spreading on surfaces exposed to pure fibronectin and various plasma solutions. The results showed that fibronectin promoted both platelet attachment and spreading on polystyrene surfaces under conditions that prevented nonspecific platelet adhesion. Fibronectin also was found to be important in platelet adhesion to polystyrene surfaces exposed to plasma solutions, but the dependence only was partial. Thus, it was concluded that the presence of fibronectin is sufficient but not necessary for platelet interactions with material surfaces.

There was a complex relationship between platelet adhesion and the concentration of plasma used to treat the material surfaces, with maximum adhesion occurring on surfaces exposed to 1.0 percent plasma. At higher concentrations of plasma, the treated surfaces supported markedly less adhesion. In relationship to plasma concentration used to treat the material surface, platelet adhesion and fibroblast adhesion showed similar responses.

The decreased adsorption of fibronectin and decreased adhesion of fibroblasts and platelets on material surfaces exposed to 100 percent plasma suggests that there are proteins adsorbed on the surfaces at high plasma concentrations that are potent surface passivating agents. Further analysis of these proteins will be of interest.

Frederick Grinnell, Ph.D., Principal Investigator

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CASE WESTERN RESERVE UNIVERSITY
Long-Term Biodegradation of Elastomeric Biomaterials
GRANT NUMBER: 5 R01 HL 25239-06

The objectives of this research are directed toward elucidating the interrelationships between biocompatibility and long-term stability of biomedical elastomers used for blood-contacting devices. By using both in vitro and in vivo environments, emphasis has been placed on determining the important biological and material factors that affect biocompatibility, biodegradation and properties of the polymers.

We have established that Biomer, which is a polyetherurethaneurea, is degraded when exposed to activated enzyme solutions containing either papain or urease for periods of up to 6 months. Papain is a plant thiolendopeptidase having broad proteolytic specificity analogous to the activity of the lysosomal enzyme cathepsin B. Polymer samples were characterized using ATR-FTIR, GPC, and mechanical properties. The products of chain cleavage were identified as free amines and hydroxyl groups. The results showed that papain was more effective than urease in degrading Biomer and that the fatigue behavior was more sensitive than mechanical properties determined in a single loading experiment.

The in vitro results suggest that polyetherurethane elastomers should be susceptible to enzyme degradation in vivo, particularly in an inflammatory environment in which leukocytes possessing the appropriate enzymes are present. Biomer was subjected to a short-term (21 day) in vivo study in which the polymer was exposed to the effects of a greatly enhanced inflammatory reaction induced by using a cytotoxic poly(vinyl chloride) film as a co-implant with Biomer. ATR-FTIR results on retrieved Biomer samples did not provide evidence of degradation. A longer study currently is under way.

Additionally, the effect of stabilizers on the biocompatibility and biostability of polyetherurethane elastomers is now being investigated.

P. Anne Hiltner, Ph.D., Principal Investigator
James M. Anderson, M.D., Ph.D., Co-Investigator
Roger E. Marchant, Ph.D., Co-Investigator

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UNIVERSITY OF WASHINGTON
Surface and Bulk Structure of Polyetherurethane
GRANT NUMBER: 5 RO1 HL 25951-05

The use of polyetherurethanes (PEU's) in medicine is rapidly increasing. Current applications include the artificial heart, heart assist devices, pacemaker leads, tubing and catheters. In the near future we will certainly see a number of PEU vascular grafts introduced into the clinic. Since it is well established that the surface structure of these polymers differs from the bulk structure and that the surface structure can be correlated with blood interactions, we have the potential to design PEU's with improved blood compatibility based upon rational design criteria. It is the overall goal of this project to understand how the bulk structure of PEU's influences the surface structure and to systematically study aspects of PEU structure that will significantly affect their performance.

Polymer synthesis efforts this year have concentrated on the production of PEU's containing fluorinated hard segments, hydrocarbon soft segments, poly-(dimethyl siloxane) soft segments, and poly(ethylene glycol) soft segments. These are all characterized by FTIR, GPC, and ESCA. For some systems, contact angle methods, SIMS, and small angle X-ray scattering (SAXS) will be utilized.

A project was completed studying the resistance of PEU's to enzymatic degradation. A number of macrophage and neutrophil enzymes were found to have some effect on PEU's, although the degree of degradation as assessed by GPC seemed to be relatively low. Hydrogen peroxide was also found to induce moderate levels of biodegradation.

A detailed angular dependent ESCA study was performed on PEU's prepared with fluorinated chain extenders. For PEU's that were extensively phase separated, only one of the phases (the soft segment) was found at the outermost surface layer. Thus, studies that implicate domains at the surfaces of PEU's for blood compatibility should be rexamined since there may be no phase separated domains at the surface layer upon which proteins and cells will interact.

Studies are continuing on the mechanism of cell death on the surfaces of PEU's in the absence of serum. Higher concentrations of soft segment in the polymer, will result in larger fractions of cells that will rapidly die. This experiment has been performed with BHK cells, 3T3 cells and macrophages with similar results. Since the effect is only noted in the absence of serum in the culture medium, the significance of this new observation for biomaterial performance is unclear.

Secondary ion mass spectroscopy (SIMS) studies continue in collaboration with Dr. D. Briggs (ICI, Wilton, U.K.). The general principles of PEU analysis by SIMS have been established and results on surface phase separation obtained with the fluorinated PEU's by ESCA have been confirmed by SIMS.

Buddy D. Ratner, Ph.D., Principal Investigator
Ron Rahman, Ph.D., Investigator
Sung C. Yoon, Ph.D., Investigator

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STANFORD UNIVERSITY
PAA Adsorption on Polymers Using TIRF and FTIR/ATR
GRANT NUMBER: 5 R01 HL 27187-04

Proteins generally adsorb onto solid surfaces from solution. The most difficult to study, and the least understood, facet of the protein adsorption phenomenon is the relationship between protein three-dimensional conformation and adsorption to solid/liquid interfaces. Conclusions about conformational effects on adsorbed proteins are often inferred from indirect results. Our recent work is directed towards using site specific monoclonal antibodies (Abs) to directly probe the conformational states of adsorbed protein antigen.

Using the technique of total internal reflection fluorescence, studies of the adsorption properties of the protein sperm whale myoglobin (Mb) onto cross-linked polydimethylsiloxane surfaces and the interactions of anti-Mb Abs with the adsorbed Mb have been undertaken. Mb was chosen because of the availability of monoclonal Abs that have been highly characterized with respect to their binding sites on the Mb molecule.

To begin, the adsorption of Mb onto polydimethylsiloxane from flowing solutions was characterized. The initial adsorption was found to be diffusion-controlled over the observed range of wall shear rates (49 to 409 s^{-1}). As time proceeds, the fluorescence intensity rises rapidly and begins to plateau. This is followed by another rapid rise. This "shoulder" in the fluorescence intensity-time relationship is not an artifact emanating from extraneous bulk solution fluorescence but represents instead a surface phenomena thought to be associated with conformational alterations in the adsorbed protein. Additional evidence to support this follows from the observation that the fluorescence intensity at which the shoulder occurs is independent of the Mb solution concentration. Over long periods of time (several hours), a slow increase in the fluorescence intensity is observed which is not due to the adsorption of additional protein and is also not caused by long-term exposure of the surface to the laser radiation. This long-term signal increase is also considered to be a manifestation of a conformation change of the surface absorbed Mb.

With this information in hand, experiments measuring the binding characteristics of anti-Mb monoclonal Abs to surface adsorbed Mb have begun. Experiments with one of these Abs reacting with Mb which has been adsorbed for 10 hours show that: (1) a reversible equilibrium exists between the Abs in solution and the surface adsorbed Mb, (2) the surface adsorbed Mb molecules are heterogeneous with respect to their binding affinity with this Ab, (3) only a small fraction of the adsorbed Mb molecules (about 0.07) are in a form that is recognized by the Ab, (4) the initial adsorption of the Ab to the adsorbed Mb layer is kinetically limited. Further experiments with Abs specific to other sites on the Mb molecule should indicate whether these are general trends or if they depend on the binding site location.

Channing R. Robertson, Ph.D., Principal Investigator

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BAYLOR COLLEGE OF MEDICINE
Effects of Shear Stress on Red Blood Cells
GRANT NUMBER: 5 R23 HL 30834-03

A potential limitation of devices such as extracorporeal circulation pumps or the artificial heart is shear induced damage to red blood cells (RBC), white blood cells, and platelets. Our studies have focused on shear induced RBC damage and hemolysis of normal erythrocytes and of erythrocytes from patients with sickle cell anemia. We have previously shown that shear stresses developed in a concentric cylinder viscometer above 1500 dynes/cm^2 cause fragmentation and hemolysis while subhemolytic shear stresses produce a damaged RBC marked by decreased deformability and increased calcium content. Shear induced RBC damage does not seem to require calcium uptake since decreased deformability measured by a Nuclepore filtration technique occurs when RBC are sheared in the presence of the calcium chelator EGTA. Also the degree of calcium uptake during shear stress and the proportion of cells hemolyzed by a given shear stress are greatly increased when the RBC are suspended in viscous media containing dextran. While calcium uptake does not explain the decreased deformability of sheared RBC, study of calcium flux during shear may provide an understanding of the underlying membrane defect occurring during mechanical trauma.

To determine whether or not shear effects on RBC are age dependent, RBC were separated according to density by centrifugation at 30,000 g in plasma for one hour at 30°C. Top fraction cells obtained in this way are younger than the more dense bottom fraction cells. When subjected to shear stress, the less dense top fraction cells showed much greater calcium uptake and hemolysis than the more dense bottom fraction cells. Since hemolysis due to artificial circulation occasionally requires transfusion support, these results are of interest as they imply that transfusion of dense fractions of blood may be more beneficial. We are now studying the RBC age dependent effects of shear stress on RBC deformability to determine if the change in deformability of young RBC accounts for the decreased deformability of the whole population of shear damaged cells.

In collaboration with Dr. Suzanne Eskin, the interaction of sheared RBC with human umbilical cord vein endothelial cell cultures was studied. Sheared RBC were perfused at a constant flow rate for 3-5 minutes through a parallel plate flow chamber in which endothelial cells grown to confluence on a glass slide formed the base. After a rinse period of 20 minutes at the same flow rate the number of adherent cells remaining were determined by video microscopy. When compared to control cells there was a three fold increase in the number of adherent sheared RBC. A possible implication of these results is that shear induced damage results in increased adherence of RBC to endothelial cells in vivo. This property of sheared RBC together with their decreased deformability may contribute to the thrombotic complications of artificial circulation.

Mark M. Udden, M.D., Principal Investigator

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UNIVERSITY OF UTAH
Protein Adsorption by Polymer Waveguide Optics
GRANT NUMBER: 1 R23 HL 32132-01A1

One of the established optical techniques for characterizing proteins adsorbed at the solid/liquid interface is Total Internal Reflection Fluorescence (TIRF). Waveguide Evanescent Streak Excitation (WESE) utilizes an integrated optics modification of the evanescent excitation principle of conventional TIRF. The waveguides used are 1-3μm transparent polymer films spun-cast onto glass substrates. WESE provides: (1) a highly defined streak of evanescent excitation at the polymer surface and (2) a stronger interfacial evanescent intensity (per unit incident intensity) than that obtained with TIRF.

Monolayers investigated to date are: (1) solution adsorbed fluorescently labeled proteins and (2) Langmuir-Blodgett deposited cyanine dye-fatty acid derivatives. The results have shown: (1) good signal to noise ratios with very low laser power (< 5 mWatts), (2) reduced photobleaching, and (3) an excellent agreement between computer calculated surface field intensities and the collected fluorescence signal strength observed as a function of mode structure (surface field intensity) and monolayer coverage (surface fluoropore concentration). All spectra have been collected at the polymer/ air interface due to the bulky nature of the prism coupling technique. It is my opinion that the optimum waveguide system will ultimately utilize a butt-coupling of light into the polymer film using optical fibers to make the system streamlined and flexible enough to be compatible with the polymer/ liquid interface. The effort to employ fiber coupling is currently under way.

William M. Reichert, Ph.D., Principal Investigator

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BIO-METRIC SYSTEMS, INC.
Anatomical Substitutes With Proclivity for Cell Lining
GRANT NUMBER: 2 R44 HL 32382-02

Biomaterials are needed for developing a wide variety of devices for implanting in the human body. A major difficulty is found in acquiring a biocompatible surface in combination with the required physical properties stable over a long period of use in the body. A major advance in biomaterials technology would result from the ability to readily tailor the surface of preformed physically optimized implant devices, to provide the proclivity for rapid overgrowth of a stable natural cell surface lining.

During Phase I, the feasibility of this approach was demonstrated. Fibronectin (FN) and laminin (LM) are potent stimulators of cell attachment and migration in vitro. FN, LM, and combinations of these proteins were coupled to the surface of plastics using heterofunctional crosslinking photoreactive reagents. Plastics (sheets and tubing) studied during this project include polyvinyl chloride, polypropylene, polystyrene, polyurethane, and polytetrafluoroethylene.

Preliminary studies using bovine and human endothelial cells suggest that these covalently coupled factors stimulate cell attachment and overgrowth on the surface of artificial vascular plastics. Current Phase II studies are being carried out to optimize coupling agents and spacer lengths. Factors currently being studied include fibronectin, laminin, albumin, collagen, endothelial growth factor, and combinations of these factors.

If this reagent technology is successful, a nonthrombogenic human endothelial cell lining will be possible. A nonthrombogenic biocompatible device would clearly have a significant impact upon modern surgical implant practices.

Peter Nash, Ph.D., Principal Investigator
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BAYLOR COLLEGE OF MEDICINE, UNIVERSITY OF HOUSTON
Hemorrheologic Contribution to Thrombosis
GRANT NUMBER: 5 RO1 HL 33089-02

The purpose of this research is to better understand the role of hemorrheological contributions to thrombosis using the arterio-venous hemodialysis access graft (HAAG) as a model. The five-stage research program includes 1) an animal model to study cellular and hemodynamic changes, 2) a flow model using Silastic conduits for detailed laser Doppler flow measurements, 3) intraoperative hemodynamic and anatomic measurements, and follow-up of HAAG patients, 4) pathologic studies, 5) computer modeling. The results will be used for characterization of clinical HAAG thrombosis.

The animal model comprises bilateral implantation of 25 cm lengths of 8 mm Gore-tex grafts from femoral artery to femoral vein in dogs. Animals are sacrificed at the intervals 1 day, 6, 12, 24, 40 and 60 weeks to evaluate the graft-vessel system. Measurements taken prior to sacrifice include flow-rates, pressures and velocities proximal and distal to the anastomoses and within the graft, phonoangiographic measurement of HAAG bruit and mechanical properties of the native vessels. At sacrifice silicone rubber casting of the vascular geometry is obtained for flow model construction. The entire graft and adjacent vessels are analyzed for gross and microscopic pathological structures.

Preliminary results have been obtained for 12 and 24 weeks. Hemodynamic measurements show large flows through the graft with retrograde flow in both the artery and vein distal to the anastomoses. Microscopic appearance indicates focal (up to 1 mm) disturbances of intimal and medial structures. Regional intimal thickening and smooth muscle proliferation were visible in the arterial wall up to at least 10 mm proximal and distal to the anastomosis. Small organized thrombi were present at multiple foci in arterial and venous lumens within several millimeters from the anastomoses. The graft lumen itself showed a focally thickened pseudointima with thickness up to 120 microns.

Transparent Silastic flow models are constructed to represent detailed geometry of the HAAG at different stages of lesion. The flow model is mounted in a pulse duplication system which generates physiological pressure and flow waveforms at the arterial inlet. The system provides adjustable compliance and resistance distal to the HAAG model. The entire apparatus is situated on a computer controlled transverse table for laser Doppler flow measurement and mapping. A computer model based on the equations governing pressure and flow pulse propagation has been developed. It utilizes HAAG geometries obtained from intraoperative measurements and silicone casts. Computed values of arterial, venous and graft flows and pressures agree with actual measurements. Analysis of several different HAAG geometries has demonstrated the importance of effects due to collateral circulation and incompetent venous valves. The model can determine the relative importance of different parameters including anastomotic angles, graft to host diameter ratio, tapering of the graft and vascular geometry.

George P. Noon, M.D., Principal Investigator
Ned H.C. Hwang, Ph.D., Principal Investigator (Subcontract)

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CORNELL UNIVERSITY MEDICAL CENTER
Platelet-Endothelial Cell Interactions
GRANT NUMBER: 5 R01 HL 33095-02

To study primary hemostasis under physiologic conditions utilizing patients' bloods, one must first be able simultaneously to measure "real time" production of PGI_2 by EC monolayers (ECM) and image real time platelet (plt) interaction with injured ECM exposed to flowing, normal bloods.

Bovine aortic ECM's, grown under static conditions to confluence on cover glasses, were therefore mounted in a parallel-plate chamber through which flowed heparinized (4 U/ml) human blood from a well-stirred reservoir at 37 °C and pH 7.4. Shear stress was calculated as the product of local shear rate (110 to 1600 sec-1) and blood viscosity (2.6 to 3.6 centipoise by high shear rate capillary viscometry). Chamber outflow blood samples were collected on ice into indomethacin and EDTA and centrifuged. PGI_2 in supernatent plasma was measured by RIA of 6-keto PGF_1. In 16 experiments (4 donors), we found that PGI_2 peak ($p < 0.02$) and total ($p < 0.01$) production increased markedly with shear stress.

The flow system also employs epi-fluorescence videomicroscopy. The fluorescent label is a murine monoclonal antibody directed against human plt GPIIB, together with a fluorescein-conjugated goat F(ab')2 against murine immunoglobulin; the monoclonal does not affect plt function. ECM now grown on microfibrillar collagen-coated, rectangular cover glasses comprise one wall of the same flow chamber attached to a microscope stage. By means of a center-of-gravity mount, the microscope rotates until chamber and stage are in a vertical plane, eliminating effects of red cell sedimentation. Microinjuries of width 70 $\pm$ 10 μm (mean $\pm$ SD) are created by drawing a 6-0 sterile suture across the ECM in a direction transverse to flow. Plt deposition is virtually absent upon intact and confluent ECM. On microinjury sites at an arterial shear rate of 270 sec-1, however, video recordings show both continuous adherence-embolization of plt singlets and multiplets, and net plt accumulation ($30 \times 10^5/cm^2$ at 10 minutes).

These results (1) clearly establish that EC's respond to mechanical flow forces, (2) for the first time demonstrate ECM production of PGI_2 in whole blood, and (3) show that it is possible directly to observe key events of primary hemostasis under controlled flow conditions.

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UNIVERSITY OF MIAMI
Flow-Induced Near-Wall Excess of Platelets
GRANT NUMBER: 1 R01 HL 33100-01

Hematocrit and flow are generally acknowledged as parameters that affect the thrombotic process, but the mechanism underlying their effects are poorly understood. To elucidate the physical aspects of these parameters, this work explores the distribution of platelet-sized latex beads in flow through capillary tubes. Fluorescence microscopy is used to visualize the beads because it avoids confusion of the image by red cells. One method uses a stroboscopic lamp and collects stop-action photographs of the beads at various locations in a channel flow. A second method, which is being developed, involves videomicrographs of cryosections of tubes that are previously frozen by sudden exposure to liquid nitrogen. Suspensions of washed red cells and fluorescent latex beads in dextrose/albumin solutions are used to mimic blood. Flows with set values of wall shear rate in either glass channels or polyethylene tubes are established by a syringe pump for 15 min to allow a steady state bead distribution to develop. Sets of studies for shear rates of 200 and 1600 s^{-1} indicate that this time is sufficient for full development of the profiles.

Analyses of images of both types show that when the hematocrit of the suspension is significant, e.g., over 10 percent, there is a significant increase in the number of platelet-sized latex beads near the wall. The near-wall concentration is elevated over central concentration by factors of two to six. Studies of latex-bead suspensions without red cells exhibit a slight reduction of near-wall concentration, which agrees with conventional microrheological studies and which demonstrates a crucial physical difference between flows of platelet-rich plasma and whole blood. Of particular interest are studies at 15 percent hematocrit at 1600 s^{-1} with latex beads ranging in mean size from 1 to 5 μm. These studies show that no elevation is seen for 1 μm beads suspended in dextrose/albumin solution; however, modest elevations are observed when the viscosity of the suspending fluid is increased 10 times with low molecular weight dextran. Beads of larger sizes (over 2.2 μm) have elevated near-wall concentrations. Suspensions with 15 percent hematocrit and with 2.4 μm beads exhibit near-wall elevations in the range of wall shear rates from 400 to 3200 s^{-1}. These data suggest that the events are correlated by a Peclet number $\mu S a^3/kT$, where μ is viscosity, S is the wall shear rate, a is the particle radius, k is Boltzmann's constant, and T is temperature. On this basis, the phenomenon represents a balance of shear-induced motion of platelets toward the wall, which is scaled by a^2S, and Brownian diffusion of the near-wall excess, which is scaled by $kT/\mu a$.

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BROWN UNIVERSITY/RHODE ISLAND HOSPITAL
Must All Implants Elicit A Foreign Body Reaction?
GRANT NUMBER: 1 R23 HL 34100-01

The traditional view is that all implants must elicit a "foreign body reaction" with a specific cellular or humoral chain of events leading to eventual encapsulation or extrusion. The hypothesis of this proposal is that in each biologic environment the final and permanent stage of the implant-tissue interaction is determined by the intensity, cellular, and extracellular characteristics, and duration of the initial inflammatory response. Understanding these responses will ultimately allow prediction and control of the final reaction.

The aims of this program are to:

1. Employ four chemically, well-characterized polymers. Two are Krebs cycle decarboxylic acid-derived bioresorbable polymers, and two are biodurable, polyethylene (NHLBI standard) and polyethylene terephthalate.

2. Implant these materials. Implantation is by paired subcutaneous sites, and colloidal suspension localization in lung and liver.

3. Evaluate the biologic reception. Evaluation is by light and electron microscopy, histochemistry, and morphometry.

4. Analyze the biologic reception data. Weight is placed on predictive factors to determine biologic outcome.

The notion that implantation site affects tissue reception is well accepted. The first step in this work is to define implantation site features with consideration of the subcutaneous and parenchymal sites employed in these studies. Subcutaneous site is protected, well-vascularized, distensible, and with few functional ramifications. Local surgical intervention is required. The parenchymal sites offer freedom from local surgery, are protected, and well vascularized. They are relatively nondistensible.

Harvey Sasken, M.D., Principal Investigator

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MOUNT SINAI SCHOOL OF MEDICINE
Role of Blood/Vessel Wall Components in Thrombosis
GRANT NUMBER: 7 R01 HL 35103-01

Von Willebrand Factor (VWF) is a ubiquitous protein found in plasma, platelets and the subendothelial layer of vessel walls. This glycoprotein is absent in von Willebrand's disease (VWD), and thus has been related to the bleeding observed in this disorder, but also has been associated with the reduced incidence of atherosclerotic plaque development in pigs with VWD. We have previously demonstrated that plasma VWF is necessary for platelet adhesion to subendothelium and that its absence results in an adhesion defect whose magnitude depends on the local shear rate. However, the role of plasma VWF in other platelet-related processes, as well as the importance of vessel wall VWF and platelet VWF are little understood.

We have utilized an annular perfusion chamber to expose blood to de-endothelialized vessel segments from rabbit aorta. After exposure of native (unanticoagulated) or anticoagulated blood, platelet and fibrin deposition on the vascular surface are evaluated morphometrically. Platelet-subendothelial interactions are distinguished from platelet-platelet associations leading to thrombus formation by the evaluation technique.

We have investigated three aspects of platelet-vessel wall interaction in flowing blood: (1) the role of VWF in platelet-platelet aggregate formation leading to thrombus formation; (2) the importance of subendothelial VWF in platelet adhesion on vessel walls; and (3) the formation and function of vessel wall VWF following re-endothelialization of injured blood vessels.

We have found that: (1) VWF and Factor VIII (clotting protein) participate in the growth of platelet thrombi in a shear-dependent manner with high shear rates (greater than 1300 sec^{-1}) requiring VWF for normal thrombus formation and low shear rates (less than 650^{-1}) requiring Factor VIII; (2) vessel wall VWF mediates the attachment of platelets to subendothelium in a manner similar to plasma VWF; and (3) hyperplastic vessel wall attracts reduced quantities of adherent platelets and virtually no platelet thrombi, however, the lack of platelet reactivity is not related to levels of VWF present at the interface.

Vincent T. Turitto, Sc.D., Principal Investigator

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Mechanical Circulatory Support

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NIMBUS, INC., AND CLEVELAND CLINIC FOUNDATION DEPARTMENT OF ARTIFICIAL ORGANS
Thermal Ventricular Assist System
CONTRACT NUMBER: N01-HV-28001

This program is being conducted by Nimbus, Inc. in association with the Cleveland Clinic Foundation (CCF). The objective of this program is to develop a fully-implantable, thermally-powered, left ventricular assist system (LVAS).

The Thermal LVAS consists of an energy converter, variable volume device, thermal management subsystem, energy transmission components, and the CCF intrathoracic blood pump. The energy converter components consist of a modified Stirling cycle engine, pneumatic controls, and actuator, which convert thermal energy into mechanical energy. The required thermal energy is obtained by periodically "charging" an eutectic fluoride salt, i.e., by supplying the heat of fusion via an electric resistance heater contained in the engine. Transmission of the electrical energy to the energy converter is across the skin through the energy transmission components which consist of an external primary coil and implanted secondary coil. The thermal energy stored through the phase change of the fluoride salt constitutes a thermal battery capable of powering the system for eight to ten hours. Thus, after a recharge period of approximately one hour, the patient is able to move around freely without being tethered to an external power source.

The development effort has as its objective a two module clinical system. One module, consisting of the blood pump, energy converter and variable volume compliance device, is located in the thorax. It occupies a volume of 720 to 815 cc of which 405 to 500 cc is intrathoracic. The engine/salt module is located subdiaphragmatically and occupies a volume of 500 cc.

Four system configurations are being built and tested in support of the clinical system: the In Vivo System, MK-9 System, Thermal Salt System and Endurance System. The In Vivo System was built to permit component development, and is powered by a MK-8 engine. It has been tested in vitro and in vivo. The MK-9 System is a vehicle for the development of the MK-9 engine. The MK-9 engine has been tested on the engine test stand, but has required extensive rework. The thermal salt system uses the MK-9 engine in a workhorse version of the clinical system. Three thermal salt systems are being built. The endurance system is an older system powered by a MK-8 engine and has as its objective continuing test of fatigue and wear sensitive components.

In addition to test of the endurance system, life tests are being conducted on engines, actuator gas piston rings, the variable volume accumulator, and blood pump diaphragms. In vivo tests of the blood pump and variable compliance device continue.

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UNIVERSITY OF WASHINGTON
(CLEVELAND CLINIC FOUNDATION)
(WHALEN BIOMEDICAL INC.)
Development of a Thermal Ventricular Assist System (TVAS)
CONTRACT NUMBER: NO1-HV-28002

The objective of this continuing program at the University of Washington Joint Center for Graduate Study (JCGS) is to develop a permanently implantable Stirling/hydraulic power source to operate ventricular assist or full-heart replacement blood pumps. PVAD Model 12A and 12C blood pumps are being refined under subcontract to Whalen Biomedical Inc. with in vivo testing and related work conducted by the Cleveland Clinic Foundation (CCF). The System 8 engine module is planned as the final preclinical design. Component fabrication of six System 8 engine modules is continuing. Fabrication of two prototype versions, which incorporate all System 8 hardware except for the thermal storage module and vacuum insulation, was completed. System 8 Prototype 1 will be used for laboratory evaluation, and Prototype 2 will be used for in vivo testing.

A 24-day in vivo test was successfully conducted with the System 7B PVAD 12A integrated package at CCF, following the previous 30-day in vivo test. The 115 kg male Holstein calf had an excellent recovery over the 24-day test period. The system demonstrated very good synchronized counterpulsation with the left ventricle. As with the previous 30-day implant, the biological interface including thermal parameters was grossly normal during and after the implant. The next in vivo test planned for late in 1985 will use the System 8 Prototype 2 engine module with a PVAD Model 12C blood pump.

Functional and performance testing of the System 8 Prototype 1 engine has progressed well. Functional performance including the integral automatic engine output controller was excellent from the first test. The counter-balanced converter pistons were successful in virtually eliminating vibration. Initial efficiency was somewhat below expectations, with about 20 percent more heat input required than expected. This was traced to hydraulic snubber energy loss which was reduced with minor hardware modifications. The Model 12C blood pump hydraulic actuator/controller produced excellent results in a laboratory configuration and is expected to be fully integrated into the Prototype 2 system before the end of 1985. Fabrication of hardware for six System 8 thermal storage engines is progressing with operational status for all six planned during 1986.

Life testing emphasizing Systems 6 and 7 critical components is continuing. A complete System 6 engine module has operated continuously for over 2 years. Several bellows components have now exceeded 8 years of continuous testing representing more than seven billion cycles.

The current state of development provides a high level of confidence that the System 8 objectives to produce a clinically useful ventricular assist system with an 8-hour self-contained operating time for a 1-hour recharge time and a 10-year lifetime potential will be realized.

Maurice A. White, M.S., Principal Investigator (Project Director, UW)
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THERMEDICS INC., AND CHILDREN'S HOSPITAL MEDICAL CENTER
Device Readiness Testing of Implantable Ventricular Assist Systems
CONTRACT NUMBER: NO1-HV-48070

The objective of this program is the establishment of the reliability and operating characteristics of the Thermedics ventricular assist system. The data generated as a result of this program will be used to support an application for an investigational devices exemption. The system to be tested is based around the Thermedics MK-IV energy converter. This converter is powered by a low speed torque motor, has a minimum of moving parts, and is assembled as an integrated unit with the Thermedics model 14 pusher plate pump. This ventricular assist device is coupled with an implantable battery pack and controller unit, a variable volume device, and a transcutaneous energy transmission system to create a totally implantable ventricular assist system that requires no penetration of the skin. An external battery pack and electronic components are also part of the system.

This program requires fabrication of the test systems under the guidelines of Good Manufacturing Practice. Complete material and process specifications have been written for the fabrication and assembly of the devices. Complete traceability of material and manufacturing processes is maintained for each lot of parts. A manufacturing history record is kept for each device.

In vitro endurance testing takes place on mock loops with the devices immersed in 37 °C saline. Device performance is continually monitored by a system of microprocessors and a master computer. If VAS output falls below 4 liters/minute, the level established as the failure criterion, the computer will automatically relay this fact to NHLBI. Ventricular assist systems under endurance test are powered by nickel cadmium battery packs.

Systems are being characterized in vitro on an instrumented NHLBI standard mock loop and are being characterized in vivo with both chronic studies and acute catheterization studies.

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William Bernhard, M.D., Co-Principal Investigator
Stan Buczak, Co-Investigator
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NIMBUS, INC., AND CLEVELAND CLINIC FOUNDATION, DEPARTMENT OF ARTIFICIAL ORGANS
Device Readiness Testing of an Implantable Ventricular Assist System
CONTRACT NUMBER: NO1-HV-48071

The objective of this program is demonstration of clinical readiness of an implantable ventricular assist system (LVAS) utilizing an intrathoracic blood pump and an electrohydraulic energy converter. The first year of program activity has concentrated on development of documentation required for compliance with GMP, fabrication of 18 ventricular assist systems for in vitro and in vivo demonstration testing, and development and check out of the in vitro reliability test set up.

The ventricular assist system being qualified consists of: an intrathoracic blood pump displacing 200 ml of thoracic volume and featuring a biolized blood contacting surface, a parathoracic electrohydraulic energy converter located in a segment of the sixth or seventh rib space, an intrathoracic variable volume device, a transcutaneous transformer, an internal battery, an external battery assembly, and a diagnostic monitor. Principal features of the system are an absence of diaphragmatic penetrations resulting from the intrathoracic and subcutaneous location of system components; the biolized blood contacting surface, which has demonstrated good resistance to calcification and thrombus formation in long-term tests without anticoagulation and the fluid lubricated energy converter which has demonstrated 5 years of in vitro operation without failure.

Development of the basic implantable system elements was completed on the previous contract, NO1-HV-02911. They were demonstrated during a 6-1/2-month in vivo test. Development of energy converter and rectifier hybrids and the implantable harness and connectors was completed early in the current program.

Fabrication of the 18 systems has required some significant process development, particularly in the area of the energy converter manifold. These structures are fabricated by diffusion bonding a stack of thin patterned titanium sheets to form hydraulic flow passages. Computer controlled laser cutting of the sheets was used in place of the previous photoetching process. It was difficult to obtain a leak-free manifold from the bonding process. External plating with braze material and then melting the braze alloy produced a hermetic external seal as verified by helium mass spectrometer leak testing. Thin walled investment castings were developed for the blood pump inner and outer housings and the energy converter enclosure lid.

The 12-station reliability test loop was assembled and checked out. The loop provides for active synchronization of the LVAS and allows computer-controlled changes in beat rate inlet pressure and simulated aortic pressure. Data on each system are automatically recorded, and each system is continuously monitored for indications of an event/failure.

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NOVACOR MEDICAL CORPORATION (DEPARTMENT OF CARDIOVASCULAR SURGERY, STANFORD UNIVERSITY MEDICAL CENTER)
Device Readiness Testing of the Novacor Implantable Permanent Left Ventricular System
CONTRACT NUMBER: NO1-HV-48072

Primary emphasis has been on preparation for device readiness testing of the Novacor implantable permanent Ventricular Assist System (VAS). The device consists of five principal subsystems: a balanced solenoid energy converter, a dual pusher-plate sac-type blood pump, a diaphragm-type variable volume compensator, an implantable microprocessor-based electronic control and power (IECP) module, and a belt skin transformer (BST).

Activity has been focused on subsystem integration and IECP miniaturization. The IECP dynamically responds to a wide range of physiologic conditions and controls power flow from the BST or battery to the solenoid. It consists of energy hybrid circuitry for solenoid excitation, control surface-mount electronics containing a microprocessor and three semicustom integrated circuits, miniature power converters, and rechargeable NiCd batteries, all hermetically sealed in a titanium case. Implantable-grade connectors are used to attach the IECP to the BST and the energy converter.

VAS fabrication utilizes extensive manufacturing and quality-assurance systems and controls (that comply with FDA Good Manufacturing Practices) in order to assure uniform production, adherence to design specifications, and reliable long-term operation.

The design and validation of the central monitoring system and the individual in vitro test stations were completed. Each test station utilizes an instrumented mock loop designed (where possible) to inherently maintain the required test conditions (pressure and flow characteristics). Critical test parameters, such as pressures, flows, and power, are monitored using an IBM PC/XT computer with dedicated software.

In vivo ovine experiments have been conducted with continued excellent results. Several long-term experiments have exceeded 140 days, and one is currently in progress after 177 days of continuous synchronous counterpulsation.

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ABIOMED (APPLIED BIOMEDICAL CORPORATION)
MASSACHUSETTS GENERAL HOSPITAL
CHARLES STARK DRAPER LABORATORY
Device Readiness Testing of an Electrohydraulic VAS
CONTRACT NUMBER: NIH-N01-HV-48073

The program objective is to demonstrate clinical readiness through in vitro reliability testing and in vivo chronic studies. Potential recipients of such a permanent device are patients with end-stage ischemic disease or idiopathic cardiomyopathies. Twelve systems are to be placed on in vitro reliability testing with the specific goal of attaining a two-year operational life. In vivo chronic studies are to be performed to achieve 25 animal-months of cumulative experience with a mean duration of approximately five months.

The system under test is a dual-chambered seamless blood pump with trileaflet valves, fabricated using Angioflex(R), a polyether-urethane. The blood chambers are hydraulically driven. The hydraulic fluid motion is derived from an axial flow pump and a fluid-shuttling two-position four-way sleeve valve. System control is achieved through the sensing of the pressures in the hydraulic chambers. The algorithm maintains the end diastolic pressure near zero.

The major elements of this program consist of the fabrication of 18 complete devices, system characterization, reliability testing, in vivo animal experiments and explant analysis, and cadaver studies. The system under test does not require valve substitution between in vitro and in vivo reliability studies, permitting direct correlation of results between these studies.

A twelve station life-test fixture has been completed. It consists of a temperature controlled bath and individual flow loops for each device. Flow is monitored by an inline venturi. Outflow pressure is set by an adjustable fluid level column height. A common plenum supplies the twelve loops. An NSC 800 computer provides parameter sampling and failure monitoring.

Device configuration has been defined and the fabrication of test units adhere to quality control measures in order to insure uniformity. Each device is characterized to establish system performance prior to reliability testing.

In vivo characterization is in progress to define the protocols to be followed in the formal chronic studies. These include operative procedures, system and animal monitoring and explant analyses. In addition, acute characterization in the biventricular configuration is planned.

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SINAI HOSPITAL OF DETROIT
(UNIVERSITY OF MICHIGAN)
Development of a Percutaneous Energy Transmission System
CONTRACT NUMBER: NO1-HV-2921

Infection is the major factor contributing to failure of percutaneous access devices (PADs). Usually the antecedent to infection is sinus-tract formation along, or marsupialization of, the implant, due to proliferation of the epithelium. Basal cells of the epidermis proliferate on but not through the dermis. It is believed that they are prevented from doing so by the presence of the collagenous network of the dermis. To evoke this mechanism by our PAD, we are investigating techniques whereby a biological seal between the PAD and the surrounding tissue is established through autologous fibroblasts grown in vitro on the transcutaneous portion of the PAD neck. We observed that the fibroblasts form confluent multilayers and extend cell processes into the nanopores of the PAD neck. As reported earlier, upon implantation of the PAD with such an Autologous Living Coated Nanoporous (ALCON) surface, epithelial migration is usually inhibited for extended periods of time.

In this report, we present the current status of long-term PAD implants in swine, and describe the results of a feasibility study of the initial steps required to replicate this technique for human use.

Nineteen PADs were implanted, 15 ALCON PADs and 4 controls. Of the ALCON PADs, there were 5 technical and 2 actual failures, while among the controls, 3 failures occurred. One animal in each group died with an intact PAD in place. Additional details are presented in the table. Thus we find that the ALCON PAD failure rate (to July 1985) is 1 every 82 implant-months, compared to 1 every 9 implant-months in the control group.

To determine whether fibroblasts from older humans can be cultured by the same technique, biopsy samples were obtained from 7 patients (ranging from 42-77 years of age) undergoing elective surgery. All 7 specimens were successfully cultured onto polycarbonate substrates, forming confluent multilayers of fibroblasts. *

A percutaneous access device, with a failure rate of 1 per 82 implant-months in swine, shows promise as an effective means for transferring pneumatic power to an implanted heart assist system. The PAD is also potentially useful for other therapies, including continuous ambulatory peritoneal dialysis, in which, according to the National CAPD Registry, the exit site/tunnel infection rate is 1 per 20 implant-months.

Reference: Steinberg SM, Cutler SJ, Novak JW, Nolph KD. Findings from NIH National CAPD Registry: January 1985. ASAIO Abstracts 1985 p. 41.

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*SBIR Grant R43 HL 31876-01A1

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CURRENT STATUS OF SWINE PADs

PAD No	Implant Duration (days)+	Status	Clinical Observation
CONTROLS			
38	215	In situ	Skin retracted from sleeve
39	238	Expl	Gross infection
40	145	In situ	Skin retracted from sleeve
52	185**	Expl	Swine died, pyloric tumor
ALCON SURFACED			
10	186	Expl	Pressure necrosis of the skin by the flange
19	776*	In situ	
21	136**	Expl	Explanted following trauma
30	431	Expl	Pressure necrosis of the skin by the flange
31	499**	Expl	Animal died of leukemia
32	377**	In situ	
33	339	Expl	Broken sleeve
34	532**	In situ	
36	420	In situ	Detachment of the skin from the sleeve
37	201**	In situ	
41	633	Expl	Infection under the flange
46	615**	In situ	
48	517**	In situ	
49	517**	In situ	
55	314	Expl	Detachment of velour

** No clinical sign of failure
Expl Explanted
+ Implant duration to failure for PADs that failed, or to 7/10/85 for implants with no clinical sign of failure

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THORATEC MEDICAL INCORPORATED
Fabrication of Cardiovascular Devices
CONTRACT NUMBER: NO1-HV-92906

The primary purpose of this contract is to supply clinical quality ventricular assist devices (VADs) to Devices and Technology Branch investigators for clinical application. Included in the devices fabricated during the past year are new VADs, refurbished VADs, and atrial, ventricular, and aortic cannulae of various configurations. In addition, accessories, such as tool sets and electrical leads, were fabricated as required.

The VAD consists of a smooth seamless pumping sac made of segmented polyurethane enclosed within a rigid polysulfone case. Two tilting disc valves control flow direction, and the pump is pneumatically actuated by an external drive console.

To date, clinical VADs and cannulae supplied from this contract have been used at St. Louis University Hospital to support the pulmonary and/or systemic circulations for up to 3 weeks in 27 patients with severe refractory left, right, or biventricular failure. The temporary use of this VAD has allowed ventricular function in seven of these patients to improve sufficiently for subsequent device removal and hospital discharge. In one additional case, the VAD was used successfully as a bridge to cardiac transplantation, supporting the circulation for 36 hours while a donor heart was being procured.

David J. Farrar, Ph.D., Principal Investigator

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PENNSYLVANIA STATE UNIVERSITY
Left Ventricular Bypass for Myocardial Infarction
GRANT NUMBER: 5 R01 HL 13426-15

PNEUMATIC ASSIST PUMP: CLINICAL STUDIES. During the past year, our group has used the pneumatic atrial to aortic assist pump in five patients. Operative diagnoses include 5° CABG, MVR; pulmonary embolectomy; 3° CABG, MVR; 1° CABG, mitral commissurotomy; and 1° CABG, VSD. Three patients were successfully weaned from the assist pump after 4 days (right ventricular support), 7 days and 5 days (left ventricular support). Two of these patients were subsequently discharged.

The assist pump that was developed by our group is now in use in 10 centers in the USA and is soon to be available in 4 centers in Europe. In addition to the use in support of the patient following cardiac surgical procedures, the pump has been sucessfully used to support two patients prior to cardiac transplantation (left ventricular--one patient, biventricular--one patient).

MOTOR ASSIST PUMP: LABORATORY STUDIES. In vitro testing of the roller screw type assist system continues with testing of the motor, pump, transcutaneous energy transmission system, and automatic control system.

A comprehensive in vivo evaluation of the roller screw assist system was initiated this year. Four animals had a sealed system implanted with a compliance chamber and percutaneous lead. The longest surviving animal was terminated at 55 days. Three of the four systems were terminated due to leaks in the system. One leak was from a cut tube, one from a poor bond on the compliance chamber, and one from a cracked pump case. The fourth calf is alive and well 35 days post-op (7/23/85) and shows no signs of bulk flow leakage. Diffusion through the segmented polyurethane is noted and characterized by increased CO_2 and decreased O_2 concentrations within the system.

There have been no mechanical failures and no measurable wear in systems that have run for up to 40 million cycles.

ABBREVIATIONS: CABG--Coronary artery bypass grafting, MVR--mitral valve replacement, VSD--ventricular septal defect.

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PENNSYLVANIA STATE UNIVERSITY
Development and Evaluation of an Artificial Heart
GRANT NUMBER: 5 R01 HL 20356-09

Pneumatically powered artificial hearts in two sizes (110 ml stroke volume--calf model, 85 ml stroke volume--human model) are undergoing continued bench and animal evaluation. The use of filler-free silicone rubber coated inlet (atrial) connectors has eliminated pannus formation and extended animal survival. The survival time following artificial heart replacement in calves has now been extended to 9 months. Problems limiting longer survival relate to sac calcification (most prominent in high flexion areas of the segmented polyurethane sac) and growth of the animal with inadequate blood flow per kg body wt. The amount of calcification appears to be less in calves on warfarin sodium and etidronate disodium.

Six months ago, our program to employ the artificial heart as a bridge for cardiac transplant received both IRB and FDA approval. To date (18 mos), we have performed 16 heart transplants with 15 patients alive and well. We have not yet had the opportunity to employ the artificial heart in the "bridge" application, but the complete system is now available.

The cam type electric motor driven total artificial heart has been implanted in four calves over the past year. In the first calf, an undersized retainer was employed and caused contact between the rotor and stator causing termination at 10 days.

In the other three experiments, extreme difficulty was encountered in oxygenation at 2 hours while on cardiopulmonary bypass. Two of the animals never emerged from anesthesia, and the third animal never fully recovered and died 23 days postoperatively. The cause of the poor oxygenation has been traced to the use of a new hollow filter oxygenator.

The smaller lighter rollerscrew total artificial heart has nearly completed preimplant in vitro testing, and implantation of the device is planned for late 1985.

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CLEVELAND CLINIC FOUNDATION
Biventricular Assist and Replacement Studies
GRANT NUMBER: 5 RO1 HL 24286-06

The purpose of this study was to evaluate various control methods applicable to a completely implantable total artificial heart (TAH). Constraints on the approaches allowable included no explicit measurement of physiological variables (pressure, flow), the use of existing NIH funded blood pumps and energy converters, and simplicity. Using only a linearized hall voltage proportional to pusher plate (PP) displacement as an input, the TAH was evaluated physiologically during each of the relevant modes. These included the two ventricles operating at variable (but independent [IND] rates), or else the rate of one slaved to the rate of the other, beating either synchronously (LMS) or alternately (LMA). Although chronic steady state effects of each algorithm were studied, the main emphasis this year has been on anaerobic threshold determinations during progressive exercise on a treadmill and transient response tests of each method to afterload and preload changes. Norepinephrine and nitroglycerine were given to bring about abrupt changes in afterload, while volume infusion was used to perturbate preload. Two size pumps were employed; one with both static stroke volumes (SSV) equal (90 ml) and the other with a built-in SSV of about 12 percent larger for left.

Although earlier studies were run exclusively in the IND mode to obtain baseline data (three experiments, 108 days, 73 days, and 45 days), results this year include both intra- and inter-calf studies from three long-term preparations (206 days and 178+ days using the equal SSV TAH and 32 days using the longer stroke, for left, pump with a built-in SSV difference). Both hemodynamic and metabolic testing indicates the LMA and LMS modes to be at least comparable to the IND mode on a chronic basis. Anaerobic threshold measurement data showed no significant differences between the modes (IND 6.97 $\pm$ .87; LMA 7.0 $\pm$ .88; LMS 6.83 $\pm$ 1.01), but control calf values (natural heart in) are significantly higher 9.87 $\pm$ 1.7 ml/kg/min. System step response testing using drugs showed LMA and LMS both to be superior to IND in terms of protecting the lungs against increases in left atrial pressure. The in vivo results confirms work done both in mock loops and using a mathematical model.

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UNIVERSITY OF UTAH
Physiological Control of Electric Total Artificial Hearts
GRANT NUMBER: 5 R01 HL 24338-06

This is the third year of a continuation grant to study physiological control of the electric total artificial heart (TAH). The main objectives are to demonstrate that an electric TAH can 1) fit in the space made available by removal of the natural heart, 2) provide extremely reliable operation, and 3) provide physiologically responsive automatic control. The design methodology has been to emphasize 1) miniaturization of the energy converter (EC) and proper shape of the ventricles to maximally utilize the anatomical space, 2) mechanical simplicity to achieve reliability, and 3) preload control based indirectly on atrial pressures to achieve a physiologically responsive heart.

A reversing, miniature axial flow pump with a brushless DC motor was chosen to best meet the above criteria in terms of size and mechanical simplicity (a one-moving part EC). Elliptically shaped bases for the ventricles maximize space utilization (Utah-100 TAH). Automatic control achieves passive filling by altering motor speeds in a feedback loop to maintain consistent, mild vacuum during filling (low drift electronic pressure transducers monitor hydraulic fluid pressure). A modified pulmonic valve was used as a balancing mechanism (static backflow greater than normal to balance the right side losses with the higher left side losses and bronchial flow).

Major program accomplishments include: 1) excellent fit in the small thorax (proper fit in 10 of 12 calves, 63 to 70 kg); 2) demonstrated successful development of reversal process under full range of loads (tested in vitro under varying physiologic parameters and in vivo, including three and four week experiments); 3) achievement of consistently balanced ventricular outputs in vivo (atrial pressures in close correspondence and below 15 mm Hg) without any adverse effects from the modified pulmonic valve (in a 28-day-experiment, LDH level returned to preoperative values and plasma free hemoglobin was virtually absent); 4) in-vitro development of preload automatic control with a) a sensitive response to mean right atrial pressure ($\overline{RAP}$) (CO rise from 5 to 9 L/min while $\overline{RAP}$ changes from 0 to 7 mm Hg), b) independence of afterload, as mean aortic pressure ($\overline{AoP}$) varies from 80 mm Hg to 120 mm Hg, CO varied $\pm$ 0.5 L/min, and $\overline{RAP}$ varied + 1 mm Hg from a regression line, c) balance capability (atrial pressures <15 mm Hg with up to five percent bronchial flow).

Program accomplishments indicate that an electric TAH has the potential to fit in the human thorax, and can be produced in a mechanically simple fashion, placing a larger burden on electronics to accomplish reversal and automatic control. To further the achievement of the three main objectives, continued research should be aimed at in-vitro durability and reliability testing, and in-vivo physiologic control tests.

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UNIVERSITY OF UTAH
Pneumatic Artificial Heart Studies
GRANT NUMBER: 5 R01 HL 24561-06

The pneumatically powered total artificial heart (TAH) was studied in mock circulation, durability testing, and while maintaining sheep and calves for periods of 268 days in the calf, and 297 days in the sheep. The JARVIK-5™ artificial heart, 160 ml stroke volume (SV), JARVIK-7® artificial heart, 100 ml SV, and a newly designed Utah-100 TAH, 100 ml SV, were used in these studies. The Utah-100 TAH evolved to meet the need for a new, elliptical design to more adequately use the available anatomic space for smaller humans. All of the devices were fabricated of Biomer™, with a continuous blood-contacting surface. The blood diaphragm ruptured at 4.90, 4.75, and 3.08 years in three ventricles (the other three layers remained intact). One ventricle is still operating at 4.8 years (226,938,000 beats). The quick-connector valve-holding system that attaches the TAH to the atria and great vessels have undergone several reiterative designs and material improvements. The presently used atrial-cuff quick-connector system has virtually eliminated the previously described pannus formation. Recipients that became septic for prolonged time periods will end up with vegetative endocarditis involving the mechanical, tilting-disc valves. Gross mineralization of the flexing blood-contacting diaphragms has not been observed with improved solution casting in the clean room. The hearts were monitored with the COMDU™ monitor, a noninvasive system which quantitates the filling rate and volumes, and calculates the cardiac output. The filling flow curve has diagnostic characteristics yielding information about valves, diaphragm, and heart-driver--controller performance. Preliminary results in mock circulation studies suggest that the mean atrial filling pressures over a wide variety of heart driving parameters within physiologic ranges can be determined very accurately. This system must be tested in vivo. Expanded computer capabilities will permit on-line, noninvasive monitoring of stroke volumes, cardiac output, mean atrial pressures, and can be expanded to include aortic and pulmonary artery pressures, and then derive other parameters.

The implantation--transplantation grant (1R01 HL 30277-03) has long ago terminated, but the last experiment was recently finished. A calf (CHARLEY) was implanted with a TAH and maintained in a very healthy condition for 74 days. The TAH was explanted and the natural heart from its twin sister was transplanted. CHARLEY was kept as a herd sire for a commercial dairy herd, and was butchered for beef after three years and two months. CHARLEY has over 50 healthy calves and more cows are pregnant. At the time of transplantation, CHARLEY weighed 100 kg, and 810 kg at death. The transplanted heart grew in concert with somatic growth, and no organ dysfunction developed while it was sustained on the pneumatic total artificial heart.

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UNIVERSITY OF UTAH
LVAD and RVAD With Portable Electropneumatic Drive
GRANT NUMBER: 5 R01 HL 29751-02

The comprehensive development of implantable, pneumatically powered left and right ventricular assist devices for extended temporary application has continued. Major advances have occurred in the last year including extensive in vitro performance testing, cadaver fit trials, and six chronic animal implantations.

The RVAD's and LVAD's are made from a thermoforming polyurethane (Pellethane, Upjohn). The components are made using the vacuum forming process. Although originally designed to use commercial tilting disc valves, the blood pumps have been modified to accept vacuum formed monocusp and tri-leaflet polymer valves being developed in our laboratory. The 85cc version (UVAD 85) of our VAD uses size 27mm valves in both the inflow and the outflow positions; the 50cc version (UVAD 50) uses size 25mm valves. We have used two different inflow cannulae for LVAD's. The "nose cone" cannula is vacuum formed in a single piece from Pellethane. It has end ports and comes in three lengths. The "elbow" cannula uses 16mm IMPRAFLEX PTFE material to connect the insertion tip of the vacuum formed quick-connect. The reinforced graft material offers flexibility to VAD placement. Outflow cannulae are made from various sizes of woven Dacron grafting material. By using atrial sewing cuffs and larger dimeter outflow grafts, the LVAD and RVAD can become a total artificial heart for use when VAD support is insufficient. Extensive in vitro durability testing has proven that the flex life of these ventricles can be in excess of one year. Mock circulation studies have demonstrated an acceptable "Starling's Law" response for passive output regulation of these ventricles. Five human cadaver fit trials have been conducted to evaluate the quality of fit and possible locations for the VAD's. The UVAD 85 can be adequately accommodated in an average to larger adult chest. The UVAD 50 can successfully fit into smaller chests.

The UVAD 85 ventricles have been implanted four times as an LVAD and twice as a total artificial heart. St. Jude valves were used in all ventricles except the fourth LVAD which had Medtronic D-16 valves. Two LVAD animals survived 28 and 32 days before elective explantation. Inflow was drawn from the left atrium; outflow was returned to the descending, thoracic aorta. Hemodynamic studies revealed little difference in device output (5 l/min) as measured with the COMDU when pumping synchronously or asynchronously with the healthy natural heart. One total artificial heart animal survived 72 days before elective explantation followed by transplantation. A subsequent autopsy revealed no renal infarcts or major lesions of organs in this animal. Hematology data has demonstrated the existence of little or no intravascular hemolysis in our extended survival animals nor has there been thrombus formation indicating the excellent hemocompatibility of these blood pumps. We believe our in vitro and in vivo experience thus far has demonstrated that the vacuum formed VAD's are inexpensive and effective devices for eventual widespread, short-term clinical application.

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CLEVELAND CLINIC FOUNDATION
Compliance System for Implantable Blood Pumps
GRANT NUMBER: 5 R01 HL 30426-02

Every pulsatile blood pump has a volume change behind the diaphragm or pusher plate equal to that on the blood side of the diaphragm. With the integration of implantable electrical and thermal drive systems with blood pumps, methods to accommodate this variable volume must be developed.

As previously reported, lenticular-shaped, dacron-velour-covered compliance chambers showed stable, thin complaint tissue capsule formation in calves in durations of up to 2 years. The biological compatibility can be considered well established.

Permeability testing showed that sulfur hexafluoride, a nontoxic, medically used gas, would have slow permeation rates and serve well as a buffer gas in the compliance gas mixture. In vivo experiments currently under way are being used to quantify the concentrations of the physiologic gases for equilibrium conditions in a closed system and to measure gas diffusion rates. For these studies sealed nonfunctioning compliance chambers are implanted in the thorax of calves. Chambers which were initially air filled show rates of volume loss nearly double that of chambers initially filled with the SF_6-buffered gas mixture. The rate of loss, while low, is sufficient to be significant over the long term.

Integrated blood pump-compliance experiments (56 and 84 days) in which the system was implanted as sealed unit without any external lines, taps, or joints were performed. These confirmed the prior results with respect to biocompatibility, performance, and long-term diffusion of the gas contents.

Analytical studies were performed to better understand the diffusion dynamics of the system. Reduction of the data indicated that the tissue capsule had very low levels of dissolved gas; this is consistent with other tissue gas measurements in the literature. The compliance diaphragm is the main area of gas loss; while the blood pump diaphragm provides a source of make up gas from arterial blood. Efforts have concentrated on developing a compliance diaphragm of significantly lower permeability.

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MEDICAL RESEARCH INSTITUTE OF SAN FRANCISCO AT PACIFIC MEDICAL CENTER
Right Heart Interaction With Left Ventricular Assistance
GRANT NUMBER: 1 RO1 HL 32202-01A1

Right ventricular (RV) failure is a frequent (20 percent) complication associated with use of a left ventricular assist device (LVAD) for refractory cardiac failure after open heart surgery. Two potential detrimental effects of an LVAD on RV function are (1) reduced septal contribution to RV contraction due to left ventricular (LV) decompression and (2) augmented venous return from the LVAD producing volume overload of an already marginal RV. There are also potential beneficial effects, which include (1) the maintenance of coronary perfusion pressure and (2) reduced pulmonary pressures due to lowered LV filling pressures.

The purpose of this grant is to evaluate the interaction between the right and left hearts and an LVAD in a controlled study by determining RV function during LV assistance in anesthetized pigs. Detailed evaluation of global and regional RV function are being made using pressure, flow, and dimensional measurements of preload, afterload, and contractility. Data are being collected under control and LV assist conditions during experimental interventions designed to model a range of pathophysiologic and physiologic conditions. These studies are designed to complement our clinical VAD program to help us improve patient selection and treatment and ultimately to promote successful use of chronically implanted VADs for end-stage heart failure.

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NU-TECH INDUSTRIES, INC.
Miniature External Drive for Jarvik-7 Blood Pump
GRANT NUMBER: 1 R43 HL 32400-01

The pneumatic drive system of the Jarvik-7 artificial heart used in the first human implant was the size of a bookcase and weighed nearly 375 pounds. The patient was always tethered to the device. The mobility of a patient connected to such equipment is severely limited, and therefore not acceptable for long term support. Improvements have been made in the size and weight of support systems, and recently a portable pneumatic system, the Heimes Driver, was used to allow temporary mobility to an artificial heart recipient.

To provide the patient a near normal "quality of life", the artificial heart drive system must be highly reliable, completely portable and configured to avoid social embarrassment. The drive system must be easily operated by the patient. There must be no hindrance to the patient's mobility. The patient must be free from concern over the public acceptance of the device. With such attributes, the system will lead to popular patient and public acceptance of the artificial heart.

As an alternate to the pneumatic systems, a hydraulic drive system is being developed for the implanted Jarvik-7 blood pump. The hydraulic system will be powered by batteries, be controlled by a small electronic package, and be connected to the patient with tubing similar to that of the pneumatic systems. The prime advantage of this new system is its size and weight. In the Phase I effort a miniature external hydraulic drive system was constructed in a belt mounted configuration which allowed it to be easily carried by the patient. The belt mounted unit included a backup battery, for temporary power when the system is disconnected, and a main, rechargeable battery was configured into a man's vest. The entire system weighed 10 pounds. During in-vitro testing, the new system powered a Jarvik-7 blood pump, connected to a mock circulation system, at cardiac outputs equal to those of the pneumatic systems.

Future development will further reduce the system's size and weight. The target size of the belt mounted unit is 25 cubic inches, and the target weight is 5 pounds, including the vest mounted battery. The fully developed drive system will be reliable and easily operated by the patient, completely portable and nearly inconspicuous in its belt and vest mounted arrangement.

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NU-TECH INDUSTRIES, INC.
Implanted Sub-Miniature Left Ventricular Assist Device
GRANT NUMBER: 1 R43 HL 33038-01

Current methods of direct blood pumping, including the heart-lung machine and the intra-aortic balloon pump, have very limited operating durations because of either accumulated blood damage or inadequate cardiac output. Also, some methods require that the patient continue with an open chest which leads to less comfort, more risk of infection, and the need for respirator assistance.

In Phase I, a sub-miniature motor and pump assembly (approximately the size of a D battery) has been designed and constructed. It will be in-vivo tested to determine the feasibility of using the device submerged directly in the blood stream to pump blood in a chronic nonpulsatile mode as a short term left ventricular assist device. Three such tests, using dogs, are planned. The tests are primarily intended to detect any blood damage caused by the presence and action of the motor pump, and to reveal any effects the blood might have upon motor pump operation. Alternate motor pump materials and coatings will be selected and tested in search of compatibility.

Preliminary work shows the motor bearings are affected by the saline condition of the blood. Various bearing materials and configurations are being evaluated for functional reliability. A special bearing will be required for this application and its design is in process.

The Phase II goal is to obtain a pump that 1) won't cause undue damage to the blood, 2) will be implantable allowing the chest to be closed, and 3) will provide cardiac support for up to 96 hours. The pump will have fewer parts, and be much smaller and much simpler than other left ventricular assist devices. The small size of the device allows ease of insertion and lends itself to closure of the chest, leading to improved patient comfort and a lower risk of infection.

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ELECTROCHIMICA CORPORATION
High Energy Stabilized Nickel-Zinc Battery Development for VAS
GRANT NUMBER: 1 R43 HL 34209-01

The development of a high energy density sealed battery system for VAS and similar devices has been recently initiated under a Phase I SBIR grant. This system offers the promise of achieving energy densities 60-100 percent greater than currently available for nickel-cadmium cells.

While the concept of a nickel-zinc battery is rather old, it was not possible in the past to obtain a good charge-discharge cycle life due to the unfavorable behavior of the alkaline zinc electrode, resulting in dendrite electrocrystallization during charge, in electrode shape change and densification. The result has been that such cells typically failed after 100-150 cycles.

As a result of the recent development of a new approach and new electrolyte system by Electrochimica Corp., the dendrite formation has been eliminated and the shape change and densification greatly reduced. This new stabilized nickel-zinc battery system has demonstrated, in vented cells, a cycle life of 600-1,000. The long-range objective of the present program is to develop the chemical and structural modifications of this new stabilized nickel-zinc battery system to permit its sealing. This includes the recombination mechanism for oxygen formed during a cell overcharge. Initial performance data for both flat and cylindrical sealed cells for the new stabilized nickel-zinc chemistry will be presented.

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NU-TECH INDUSTRIES, INC.
Optimized Jarvik Electrohydraulic Artificial Heart
GRANT NUMBER: 1 R43 HL 34935-01

Miniature brushless DC motors have found application in artificial heart hydraulic drive systems. Nu-Tech motors are used in the Jarvik Electro-hydraulic Energy Converter which is used to power the hydraulic Jarvik-7 artificial heart. The hydraulic drive system pumps a fluid back and forth between the heart's two artificial ventricles. Such performance requires continuous and rapid reversal of the motor to power the pump in alternate directions. The drive system includes an electronic controller which insures that appropriate voltages are applied to the motor to generate the proper speeds and to cause motor reversal.

The current flow can fluctuate widely during motor reversal and can often strain the capability of the controller, motor, and battery. The erratic current can result in irregular pump operation, overheating in the controller, and excessive battery drain. The result is a reduction in the overall system operating efficiency, the duration of the battery, and the life of the electronics.

The drive systems developed to date have employed various techniques which attempt to smooth out and limit (if only moderately) the current flows during the reversal period. Effort is now being concentrated on the problem of current variations in an attempt to make significant improvements in efficiency and in operating smoothness. Nu-Tech is applying the methods of dynamic braking, coasting and plug reversing with pulse width modulation, to avoid the frequent current spikes and to minimize the power required to reverse the pump. Such optimization will minimize the demands on the battery and lead to an optimum trade-off between duration of operation and system weight.

Concurrent with the motor/pump efficiency improvement, construction of a high energy density battery pack is being performed. A battery pack of prototype zinc-air cells is being configured and will be tested. Also, a prototype fuel cell which has potential application in this project will be tested. The zinc-air cell has a watt-hour per pound rating that is 10 times greater than the conventional nickel cadmium cell, and the fuel cell has a rating 20 times greater than the nickel cadmium cell.

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McGILL UNIVERSITY
Skeletal Muscle Powered Cardiac Assist: The Current Status

Renewed interest in utilizing skeletal muscle to power cardiac assist devices can be attributed to recent advances in two areas, namely, the advent of microcircuitry allowing the development of an implantable device which synchronizes and modulates the contraction pattern of the skeletal muscle and the recent development in muscle physiology which demonstrates the feasibility of converting muscle fibers to more fatigue-resistant population.

Our study has been to develop a programmable, synchronized pulse train electric stimulator, which can induce skeletal muscle contraction analogous to that for myocardium during selected periods of cardiac cycle. This device has been miniaturized by the Medtronic Company and is being made implantable for chronic studies. The device has been used in acute experiments to study a variety of cardiac assist modes, including the myocardioplasty, left ventricle-to-aorta balloon conduit in a LVAD mode, and an extra-aortic balloon pump for prolonged counter-pulsation. The latter mode of extra-aortic balloon pump assist is currently the least invasive, and hemodynamically effective.

Synchronously stimulated skeletal muscle for myocardioplasty can be shown experimentally to augment left ventricular function and has been successfully applied in a clinical patient. The use of skeletal muscle as the source of energy for LVAD can at least provide partial bypass, although whether it can completely replace the left ventricular function is not clear at present.

Transformation of the skeletal muscle fibers to type I fatigue-resistant population was initially achieved by electrical stimulation at 10 Hertz frequency for several weeks. Recent studies indicate that the frequency requirements are not absolute, and the type of pulse train electrical impulses used for the studies described above have been found to be effective also in transforming muscle fibers. Current study is to proceed with chronic experiments, evaluating both the hemodynamic efficacy as well as the "working transformation" of the muscle fibers in response to the electrical stimuli. The optimal stimulation parameters elucidated in normal mixed fiber skeletal muscles are being re-evaluated in muscles which have been almost completely transformed into fatigue-resistant fibers. Convergence of these studies may provide a new totally implantable cardiac assist system, which should be useful in patients with chronic heart failure, short of undertaking total cardiac replacement either with an artificial heart or with transplantation.

Ray C.-J. Chiu, Principal Investigator

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Calcification of Prosthetic Materials

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MAYO FOUNDATION
Inhibition of Calcification and Thrombosis in Tissue Valve
GRANT NUMBER: 5 R01 HL 28974-03

One hundred and fifty-three Holstein calves were implanted with 25 mm Ionescu-Shiley pericardial tissue valve prostheses in mitral annulus and two 2 cm x 2 cm glutaraldehyde-fixed pericardial patches under the skin in the abdomen. Calves in the control and diphosphonate (DP) treated groups (5 mg/kg/day, subcutaneously) were killed at 1, 14, 30 and 90 days post valve prosthesis implantation. After harvesting the valve and dissections, regional platelet thrombosis was quantified with ^{111}In-labeled platelets (platelet/mm^2 of leaflet). Platelet and fibrinogen consumption was further quantified by platelet survival with ^{111}In-platelets and ^{125}I-labeled bovine fibrinogen, respectively, at seven days preoperation, immediately postoperation, 14 and 45 days post-implantation. Total calcium in four zones of leaflets and sewing ring was determined by atomic absorption spectrometry and further checked by energy dispersive x-ray analysis (Ca, P). Endothelial cell coverage of leaflets was monitored by scanning electron microscopic technique. Results of regional calcification in the control and DP-treated calves at 1, 14, 30 and 90 days post-implantation showed a decrease in platelet thrombosis and increase in calcification. Platelet thrombus and collagen in pericardium calcified at an exponential rate. Calcium level in subcutaneous pericardial implant is much lower than the pericardial leaflet in valve prostheses.

Although the results indicate that DP treatment reduces calcification, in all sections of leaflets at 90 days the side effect (inhibition of bone growth) is severe enough to prevent its clinical trial. We have recently developed a new technique of processing collagenous tissue. This involves removal of antigenic proteins with detergents, immobilization of diphosphonate derivatives, stabilization of drug-collagen bond by borohydride reduction and removal of excess glutaraldehyde before implantation. This processing of pericardial tissue promotes spontaneous endothelial cell coverage of leaflet. High dose aspirin (25 mg/kg/day, oral) did not reduce platelet thrombosis; suppression of inflammation increased the bacterial infection of prosthesis. We have also used ^{125}Iodine-labeled antibody (rabbit antiserum against Type I bovine skin collagen) to evaluate collagen coverage of sewing ring and leaflet from the proliferating fibroblast. ^{111}In-labeled pure granulocytes permitted us to quantify granulocyte infiltration in the initial healing phase. These techniques will be useful to evaluate a new generation of tissue valves and develop ideal valvular prostheses.

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UNIVERSITY OF PENNSYLVANIA
Calcification Mechanisms in Cardiovascular Prostheses
GRANT NUMBER: 5 R01 HL 29979-04

Preformed aneurysms of glutaraldehyde fixed bovine pericardium were inserted into myocardial openings in the right atrium and right ventricle of 43 young sheep for 2 to 189 days. The pericardium was mounted on preformed chambers made of rigid flanged epoxy rings and a flexible polyurethane back. Implantation was done during 30 second inflow venous occlusion. Intrinsic mineralization developed in 18 of 29 animals with pericardium initially processed in phosphate buffered (PB), 2 percent glutaraldehyde at pH 7.2. It did not occur in 13 animals with pericardium initially processed in acetate buffered (AB), 2 percent glutaraldehyde at pH 5.6. Extrinsic mineralization was observed in organizing thrombi or neointima on both types of pericardium.

The two types of calcific deposits had distinct radiographic features and the locations were confirmed histologically. Extrinsic mineral occurred in white raised organized thrombi or neointima and had a speckled or reticulated pattern in radiographs. Intrinsic mineral appeared as a homogeneous, localized, radiodense area of variable size with sharply delineated borders.

All animals with phosphate buffered pericardial implants for 60 days or more had some degree of intrinsic mineral. It occurred primarily at the periphery of the implants over the epoxy flange. Intrinsic mineral was also present in the central zone in one-third of mineralized specimens. When only a trace of mineral was present, it was usually limited to the ventricular implant and was located in the flange area. When moderate to severe amounts of mineral were present, there was no substantial difference in the degree of intrinsic mineralization between ventricular and atrial implants.

Mineralization of subcutaneous implants was noted in about half of the animals, but the occurrence and distribution were not predictive of mineralization in the central part of the cardiac implant.

Chemical analyses are incomplete, but results for calcium and phosphorus indicate large amounts in areas that were positive for mineral in radiographs. Morphologic studies have demonstrated the importance of cellular involvement in the initial phase of mineralization. In severe cases, there appears to be mineral involving collagen fibers, as well as cellular debris. But in peripheral areas and specimens with only trace amounts of mineral, the mineral was restricted to cellular localizations and small subcellular bodies. Transmission electron microscopy has shown mineralization predominantly in the nucleus of fibroblasts in the pericardium.

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CLEVELAND CLINIC FOUNDATION
Calcification in Blood Pumps
GRANT NUMBER: 1 R01 HL 30005-01A1

We hypothesize that calcification in tissue valves, vascular grafts, and blood pumps is dystrophic calcification occurring secondarily in degenerating cellular deposits.

Blood pumps lined either with glutaraldehyde-treated, smooth gelatin surface or polyester flock have been implanted up to 7 months. The extent, location, and nature of calcified lesions formed on these two different materials have been studied and compared using x-ray, histology, and electron microscopy with elemental analyses. Four different tissue valve materials, i.e., human dura mater, bovine aortic, porcine aortic, and bovine pericardium, have been utilized in these blood pumps and compared. The in vitro tests have focused on calcifiability of degraded blood cells serving as the nidi for calcification. A series of in vitro tests were conducted to explain the in vivo observation that calcification starts in the deeper layers of the pseudoneointima or valve tissues but not from the surface of these materials. Bovine plasma was filtered through the tissues to see how various humoral factors affect calcification.

Calcification, when observed, on the gelatin surface, always started in the localized deposits of blood cells. Calcium scans of the gelatin surface without deposition did not disclose calcium phosphate. Calcification on the flocked surface also involved degraded blood cells in the neointima, but did not involve the polyester fibrils. Leukocytes, platelets, and erythrocytes served as nidi for calcification in both in vivo and in vitro experiments. Plasma membranes, nuclei, and cellular organelles appeared to be the initial calcification sites. Various valves showed calcification starting in collagen and elastic bundles and host-derived blood cells insudated into the tissue. The valves used in the left side of TAHs always showed more extensive calcification and calcium content when compared with the right side valves, suggesting that mechanical stress is a promoting factor in calcification. Plasma filtrates through valve tissues and fibrin showed higher P/Ca ratios and calcified blood cells more quickly than the native plasma. This finding supports our previous hypothesis that vulnerability of young calves or humans to dystrophic calcification is due to their high plasma phosphorus levels.

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ABIOMED
Mechanical Etiology of Calcification
GRANT NUMBER: 5 R01 HL 30013-03

There is evidence in the literature which suggests a correlation between mechanical factors (shear stress, mechanical strain) and host defined blood chemistry factors (Ca:P, osteocalcin) on the intrinsic calcification of blood contacting materials used in cardiac prostheses. The purpose of this study was to elucidate the mechanical/biochemical mechanism(s) affecting calcification in the nonanticoagulated calf using left ventricular to descending thoracic aorta valved conduit implants. The conduit wall and valve blood contacting surfaces were fabricated from a single smooth surfaced polyurethane elastomer. Physiologic flows were maintained in the conduits by constricture of the ascending aorta. The clinical condition and health status of each calf was evaluated daily through vital signs and auscultation of the conduit prosthesis, and bimonthly with a complete hemogram and a serum chemistry profile. Osteocalcin levels were measured pre-operatively and throughout the implant duration.

Eighteen surgical procedures were performed with elective conduit retrievals occurring at 4,7,10,15,17, and 22 (4) weeks post implantation. Congestive heart failure due to fibrotic overgrowth of a misaligned inflow conduit occurred in four calves between 48-75 days post-op. Serum osteocalcin levels fluctuated with the clinical course of each calf as well as the serum alkaline phosphatase. During the immediate post-op interval and in the presence of evolving CHF, osteocalcin levels decreased significantly. In contrast, calves having a sound clinical history with excellent weight gain had high osteocalcin levels. Fluctuations in osteocalcin and alkaline phosphatase were attributed more to generalized pre or post-op health status than to age.

Two distinctly different types of calcification have been identified. Gross (macroscopic) calcification was found at regions of mechanical strain (leaflet flexure) and in regions of low flow (leaflet commissures). The second type of calcification was found on the leaflets and conduit walls proximal and distal to the valve. The deposits were observable only by light and scanning electron microscopy and appeared as low profile individual or interdigitated plaque-like spherules. The plaques showed more dendritic growth on the flexing components than on the non-moving conduit walls. Plaque density was affected by whether the blood contact surface was air-cured (less) or mandrel-cured (more). The density was also directly related to implant duration (75 days earliest detection) and the health status (growth) of each calf throughout the implant duration. The mechanism(s) affecting this calcific phenomenon are presently under study by TEM. The spherules are firmly bound to the surface and do not appear to be affected by surface voids.

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AMERICAN DENTAL ASSOCIATION HEALTH FOUNDATION
Prosthetic Materials in the Cardiovascular System
GRANT NUMBER: 5 R01 HL 30035-03

Mineralization of bioprosthetic devices presents a serious problem. Mechanisms of mineral deposition/inhibition are not well established, and this inadequacy creates an impediment which must be overcome for successful application of artificial organs. The genesis of the crystal chemical properties of a calcium phosphate cardiovascular deposit lies in its structure at the atomic level.

We report here the results of a comprehensive effort to characterize these materials through the use of a variety of physicochemical procedures (XRD, IR spectroscopy, SEM, polarized light microscopy, determination of thermodynamic and kinetic dissolution properties). Purified deposits (hydrazine treatment) from six bioprosthetic devices and intima of 20 aortas were used in this study. In addition, thermodynamic solubilities of defined calcium phosphate phases, $CaHPO_4.2H_2O$ (DCPD), $Ca_8H_2(PO_4)_6.5H_2O$ (OCP), and $Ca_{10}(PO_4)_6(OH)_2$ (OHAp), in native ultrafiltered serum were determined. Chemical analysis of calcified deposits (Ca/P = 1.6 $\pm$ 0.2, CO_3 = 5-10 percent) XRD and IR are in accord with a typical "carbonate-containing bioapatite," containing significant amounts of Na and Mg. The index of refraction, thermodynamic solubility data, and chemical potential plots are all in accord with OCP as a major phase. The solubility data are also in accord with β-tricalcium phosphate (β-TCP) or sesquiapatite as a principal mineral phase, excluding the presence of OHAp as a major phase. We conclude that the most probable type for both the prosthetic and intima layer aortic deposits is OCP and a continuum of carbonated and hydrolyzed products derived from precursor OCP. Ca/P ratios derived from chemical potential plots ($\sim$1.5) increased with increasing CO_2 pressure ($\sim$1.9), suggesting that carbonate is incorporated into the crystals as a part of the structure.

The new evidence presented here, that OCP is a precursor, is in accord with calcium phosphate saturation levels obtained in our studies in ultrafiltered serum. Consequently, if the activity product for OCP is not exceeded, the mineral deposition would be precluded. This has major implications concerning the formation or prevention of bioprosthetic/atherosclerotic calcification through control of the calcium and phosphate levels in blood.

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CHILDREN'S HOSPITAL, BOSTON
Gammacarboxyglutamic Acid in Cardiovascular Disease
GRANT NUMBER: 5 R01 HL 32261-04

Calcification (CA) is the most frequent cause of the failure of bioprosthetic heart valve (BHV) replacements. Experimental studies in this program over the past year have focused on the interactions of anticalcification agents with the development of BHV-CA. Ethanehydroxydiphosphonate (EHDP), which has been used in the clinical management of some metabolic bone disorders, was administered to 21-day-old rats subcutaneously implanted with BHV. The lowest effective dose of EHDP administered by daily injection was 15mg/kg/24 hours. This therapy inhibited BHV CA, but with severe untoward effects on overall growth and bone development. Attempts at either limiting the dosage of EHDP or the duration of injection therapy were not only ineffective in decreasing CA, but were also associated with adverse effects.

Because of the untoward effects of EHDP in injection therapy, experiments were carried out with controlled-release drug delivery matrices formulated with EHDP dispersed in ethylene vinylacetate (EVA). It was hypothesized that drug delivery matrices positioned next to valve implants would release low levels of EHDP sufficient to inhibit BHV CA, but far below systemically toxic levels. After initial formulation of EVA-EHDP matrices and in vitro release studies which established a prolonged extrapolated release period (>2 years), these controlled-release matrices were studied for site-specific EHDP therapy directly into BHV implants. EHDP site-specific therapy not only completely inhibited BHV CA using only 1 percent of the lowest effective EHDP daily injection dose, but also was not associated with any adverse effects on bone development or overall growth. Controlled-release anticalcification therapy was effective for up to 84 days of subcutaneous implantation, a period of time which resulted in control levels of CA equivalent to several years of clinical implantation.

Studies in progress for the forthcoming program year will pursue the concept of site-specific controlled-release for administering EHDP locally. We will study orthotopic BHV implants with controlled-release from matrices positioned around the valvular annulus. Various means of sustaining the controlled-release drug delivery will also be investigated, including variations on the polymeric matrix (polysiloxanes and polyurethanes will be used), and by varying the solubility of the EHDP (by using dispersions of the calcium and magnesium salts of EHDP). Preliminary results indicate release durations of 10 years or more will be feasible.

EHDP THERAPY: CONTROLLED RELEASE VS. INJECTION (21 day implants)

Dosage Form	N	Valve CA (ug/mg)	Percent of Normal Wt.
Injected (1mg/kg/24hr)	10	100.0±5.1	100
Injected (15mg/kg/24hr)	10	3.5±0.5	75
Controlled Release (.1mg/kg/24hr)	10	5.2±1.3	100
Unimplanted Cusp	8	2.8±0.7	--

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CHILDREN'S HOSPITAL, BOSTON
Structural Proteins in Bioprosthetic Heart Valve Calcification
GRANT NUMBER: 5 R01 HL 32346-02

Bioprosthetic heart valve (BHV) calcification (CA) represents the most frequent cause of the clinical failure of this type of cardiac replacement valve. Ongoing research in the program has demonstrated that collagen calcification and mineral deposits in devitalized BHV cells are the two pathologic hallmarks of this disease process.

Bovine pericardial BHV CA has been demonstrated to occur in subcutaneous implants (in 3 week old male rats) with an identical pathophysiology to porcine BHV CA with respect to morphologic appearance and localization of CA and the kinetics of bulk mineral accumulation. Detailed studies of the earliest appearance of pericardial BHV CA indicate that although initial deposition can be detected in devitalized cells of some specimens as early as 24 hours, it is uniformly present by 48 hours. Initial deposits resembled matrix vesicle CA normally noted in bone development.

Tritium-labeled glutaraldehyde incorporation experiments using pericardium examined the kinetics of incorporation at physiologic pH. It was demonstrated that one-half maximal levels were reached after only 1 hour's incubation and that maximal plateau levels were present by 18 hours. Glutaraldehyde incorporation and crosslinking was pH dependent with greater amounts taken up by the BHV tissue at pH's above neutrality compared with low level incorporation occurring at pH 3, which was also less stable in terms of collagenase digestibility (table 1). Implant CA (table 1) was significantly diminished in BHV pretreated with glutaraldehyde at pH 3 compared to those pretreated at pH 7.4. Although increased tissue levels of glutaraldehyde occurred after incubation at pH 10.0, the level of implant CA was virtually identical to that observed in the explants pretreated at pH 7.4. These results indicate that the cross-linking mediated potentiation of BHV CA requires glutaraldehyde incorporation to a finite threshold level of cross-link formation, beyond which, maximum CA occurs regardless of additional glutaraldehyde uptake.

The continuing studies of this program will completely characterize the initial events of BHV and collagen CA, including studies of circulatory BHV implants, and the importance of glutaraldehyde to the CA mechanism will be pursued with radiolabeled incorporation studies in both BHV and collagen.

Table 1. GLUTARALDEHYDE (GLUT) INCORPORATION AND CA OF BHV IMPLANTS

Glut Incubation (24 hrs)	N	Glut (nm/mg)	Ca++ (ug/mg)	Percent Collagenase Digested
pH 3.0	6	78.3±9.4*	9.9±6.9	98.7
pH 7.4	6	318.4±7.4*	96.7±12.3	31.7
pH 10.0	6	439.6±9.8*	92.2±4.8	31.5
Unimplanted Cusps**	8	--	2.8±0.7	25.2

*21 day implants in 3-week-old male rats.
**not pretreated with glutaraldehyde.

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Frederick J. Schoen, M.D., Ph.D., Co-Investigator

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CHILDREN'S HOSPITAL, HARVARD MEDICAL SCHOOL
Blood-Material Interactions: Calcification
GRANT NUMBER: 5 RO1 HL 32356-03

Calcification of left ventricular assist devices at the polymer pseudoneointimal (PI) interface results in compromise of the long-term function of the device. Several contributing factors to calcification on biomaterials have been delineated, including (a) mechanics of the pump, (b) biomaterial-PI and/or blood interactions, and (c) physiological status of the animal. Calcification at the PI-biomaterial interface has been postulated to involve a process of thrombus formation, degeneration of cells, accumulation of calcium binding proteins and subsequent formation of hydroxyapatite crystals.

Our group has started development of an in vitro model designed to approximate pathological calcification at the biomaterial-PI/blood interface. We have constructed a pneumatically driven device which enables us to immobilize six sterile 32 mm discs of elastomeric biomaterial, upon which vascular cell cultures are grown. The frequency and amplitude of deformation of the cell seeded elastomer can be carefully controlled by the pneumatic logic circuit, and the strain on the surface of the polymer mathematically defined. Vascular endothelial and fibroblast cells are grown on a variety of polyurethane and silicone elastomeric surfaces (i.e., Tecoflex, Angioflex, and Biomer; smooth, textured, and surface imperfections). Cellular growth on the biomaterial is quantitated by DNA content for several parameters, including (a) plating or attachment efficiency, (b) population doubling time, and (c) final cell density. Cellular response to the biomaterial, evaluated by phase contrast microscopy and histology, as well as scanning and transmission electron microscopy has shown that endothelial cells have a stellate appearance with numerous long processes when subconfluent.

Biomaterial-cellular interactions lead to cellular degeneration under a variety of physical and chemical influences, which in turn result in calcific deposits that impair pumping efficiency. The nutrient media of the cultures is a high calcium and phosphate containing media (i.e., modified BGJb) to aid in the induction of calcification. The formation and resorption of calcific deposits can be monitored in this system, and the effect of a variety of physical and chemical parameters on the process determined. In addition, impaired cellular activity (i.e., protein synthesis, division, etc.) can be monitored as a function of mechanical stress (stretching frequency and amplitude). Cellular damage during mechanical stress is monitored by lactate dehydrogenase release versus control. Calcification is evaluated in the experimental and control cultures microscopically (von Kossa staining) and biochemically (^{45}Calcium uptake). Overall, this in vitro system of LVAD calcification is more readily manipulated, and should provide an accurate in vitro model for pathological calcification of biomaterials in a "pumping" environment.

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Small Vessel Prostheses

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UNIVERSITY OF WISCONSIN
Protein and Thrombus Deposition on Vascular Grafts
GRANT NUMBER: 5 R01 HL 21001-08

Recent studies have indicated that the protein adsorbed at the biomaterial-blood interface play a significant role in thrombus deposition. We have recently designed a FTIR/ATR flow cell with a nearly uniform wall shear rate as a tool to study protein adsorption on biomedical polymers. The polymers are coated on a germanium ATR element. The first set of experiments studied albumin (10 mg/ml, pH 7.35) adsorption and desorption on Biomer at controlled wall shear rates of 0, 50, and 450 sec^{-1}. The kinetics of adsorption and desorption were followed by measuring the height of the 1550 cm^{-1} absorbance peak. The contribution of supernatant (non-adsorbed) protein within the evanescent wave was accounted for. Results show that adsorption is kinetically controlled at this solution concentration. Between 10 and 120 minutes of contact, the rate of adsorption at 50 sec^{-1}, was about 18 percent and 11 percent greater than the rates of 450 and 0 sec^{-1}, respectively. Adsorption did not plateau within 6 hours of contact. The desorption rate of 450 sec^{-1} was about 20 percent greater than at 50 sec^{-1}.

Another FTIR/ATR study investigated the effect of various amounts of preadsorbed albumin on the initial adsorption rate of canine fibrinogen (0.5 mg/ml, pH 7.35) on silicone rubber. The initial adsorption rate decreased linearly with increasing albumin surface concentration between 0 and 0.24 $\mu g/cm^2$ adsorbed albumin.

Other in vitro studies utilized gold bead immunolabeling to determine protein distribution and conformation after sequential protein adsorption onto different biomaterials. A polymer shunt was preadsorbed with either albumin or fibrinogen. After flushing, the same shunt was exposed to the second protein. The ability of the immunogold beads to adhere to the protein layer depends on the exposure of the antigenic sites of the protein, and thus on the conformation of the protein. Homogeneous distributions of immunogold beads were observed on poly(vinyl chloride) (PVC) and polyethylene (PE) surfaces with either fibrinogen or albumin adsorbed singly. In sequential protein adsorption, fibrinogen adsorption followed by albumin adsorption resulted in a much higher attachment of antifibrinogen gold particles compared to antialbumin gold particles. This result was obtained even though the amount of adsorbed albumin was higher than that of fibrinogen as measured by radiolabeling techniques. This suggests that the conformation of fibrinogen is altered by the presence of albumin such that more antigenic sites are exposed.

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BOSTON UNIVERSITY SCHOOL OF MEDICINE
Hemodynamics in Vascular Surgery
GRANT NUMBER: 5 R01 HL 21796-07

Delayed failure of vascular prosthetic grafts contributes significant morbidity and mortality to patients who have undergone vascular reconstructions. There is increasing evidence that graft failure is attributable to the pathologic process of intimal hyperplasia between graft and host vessel. This laboratory previously reported that hyperplasia occurs at both anastomoses, but quantitatively to a greater degree at the distal or downstream anastomoses in canine femoro-femoral grafts. To account for this phenomenon seen clinically and experimentally, we postulated that contact activation of blood components by the synthetic surface might lead to the augmentation of hyperplasia at the downstream anastomosis. The current study was designed to evaluate the role of contact activation of blood via prosthetic surface. Twelve 8 mm x 55 cm dacron carotid artery to aortic trifurcation grafts were placed subcutaneously in mongrel dogs weighing 25-30 kg. Blood flow through the graft was monitored with an electromagnetic flow meter and variable flows generated by a Rommel's snare clamp distal to the distal anastomosis. Sampling cannula were placed in the proximal and distal graft hoods. Samples of blood were taken simultaneously at 1, 3, and 24 hours and at 7 and 30 days postreconstruction. Samples were analyzed for thromboxane B2, fibrinopeptide A, platelet and white blood cell count, as well as fibronectin. Baseline samples were drawn prior to surgery through the femoral vein.

A statistically significant difference in cleavage products of thrombogenesis and platelet release was demonstrated across the grafts. Thromboxane B2 generation was greatest immediately postreconstruction with a mean proximal to distal differential 55 percent greater than baseline values. This differential was reduced by 24 hours, and by 7 days a differential could not be demonstrated. Flow reduction always resulted in proximal to distal release of thromboxane B2 regardless of the maturity of the graft surface. Fibronectin levels dropped 25 percent across the graft acutely which rebounded by 7 days. A proximal to distal increase in fibrinopeptide A was documented which was amplified by flow reduction.

In vivo interaction of blood with dacron arterial grafts causes release of thromboxane and cleavage of fibrinogen within the graft. Interaction is greatest immediately after graft placement and is stable by 7 days. Release of thromboxane and fibrinopeptide A increases as flow decreases. Contact activation of blood results in the genesis of products of thrombosis, thromboxane B2, and fibrinopeptide A. Other factors may be released, specifically, platelet derived growth factors which have their effects at the downstream anastomosis. This markers of contact activation will be of value in evaluating new surfaces and/or the efficacy of drug intervention.

Frank W. LoGerfo, M.D., Principal Investigator

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UNIVERSITY OF TENNESSEE CENTER FOR THE HEALTH SCIENCES, DEPARTMENT OF MEDICINAL CHEMISTRY AND DEPARTMENT OF MEDICINE
Surface-Active Antithrombotic Agents for Prostheses
GRANT NUMBER: 5 R01 HL 22236-06, Extended

Extensive studies were completed on interconnections between chemical structure, platelet aggregation-inhibitory potency, and cellular toxicity (Lasslo, Dillingham, McCastlain, Carter-Burks, Quintana, Johnson, and Naylor, Chemico-Biological Interactions, submitted). Relationships were examined between the molecular constitution of synthetic entities, their aggregation-inhibitory potency (as determined in ADP-induced human blood platelet aggregation), and their cellular toxicity (as assessed by their inhibition of cultured mouse fibroblast L-cell growth). Blood platelets are relatively highly differentiated bodies compared to fibroblasts which are much more primitive pluripotential cells. Effects exerted on platelets tended to reflect interactions between the molecules' aggregation-inhibitory specific functions and the platelets' corresponding target sites, while fibroblasts were generally more susceptible to the molecular constitution's hydrophobic character. The hyperbolic relationships between concentrations effecting 50 percent inhibition and slopes of concentration-response curves disclosed net activity from both specific and nonspecific receptor site interactions, with the latter being dominant, and indicated that the assays approximated equilibrium systems. Plotting logarithm values of concentrations effecting 50 percent inhibition against logarithms of reciprocal slopes for concentration response curves yielded multiple regression coefficients of $R = 0.97$ (platelet aggregation-inhibitory potency) and $R = 0.98$ (fibroblast growth-inhibitory potency).

While we are hesitant to make premature conclusions, one finds it difficult to refrain from pointing out that one of our compounds registered 21 times greater potency in blocking human blood platelet aggregation than in displaying cellular toxicity.

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Marion Dugdale, M.D., Co-Principal Investigator
Elwood O. Dillingham, Ph.D., Co-Investigator

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UNIVERSITY OF WISCONSIN
In Vivo Evaluation of Surface-Induced Thrombogenesis
GRANT NUMBER: 5 R01 HL 24046-06

The loss of patency of small-diameter vascular grafts is a major obstacle to their successful clinical application. The evaluation of blood compatibility of biomaterial vascular grafts has been hampered by the lack of methods to access thromboembolization and long-term patency in animal models.

We have conducted experiments to develop a method for the long-term implantation of vascular grafts in non-anticoagulated canine subjects, using an ex vivo shunt. The shunt, which consists of 3 mm I.D. silicone rubber tubing, cannulates the left external iliac artery and is exteriorized through a fenestration in the skin located at the end of the 13th rib. The shunt is then returned in the same fashion to the iliac vein on the other side of the animal. The test materials can be placed in the portion of the shunt which extends over the back of the animal and can be removed for scanning electron microscopy or radioisotope counting when desired. Four surgeries have been performed with limited success. Two experiments were terminated due to loss of patency of the shunt. One animal exsanquinated after biting through the shunt. In the fourth animal, the silicone rubber shunt remained patent for 9 weeks. At 9 weeks, the cannulation site in the iliac artery became obstructed by thrombi, probably due to blood turbulence at the junction, and the experiment was terminated.

This chronic shunt model has the potential to provide more temporal data than the commonly used interpositional grafts which often provide only an end point determination of patency. It also allows the long-term testing of different materials in the same animal without multiple surgeries which would minimize animal-to-animal variation.

In other studies, acute (short-term) ex vivo experiments were done to evaluate the blood compatibility of polyether-urethane ionomers. Deposition of radiolabeled platelets and fibrinogen was used as a measure of thrombogenicity. These materials were synthesized in our laboratory and contained: (a) different hard/soft segment ratios or (b) a hard segment chain extender which had been ionized to form an anionomer, a cationomer, or a zwitterionomer. The surface properties were examined using contact angle, ESCA, and FTIR.

Lower surface soft segment concentration was correlated with increasing thrombogenicity for the neutral urethanes. Ionization altered both thrombogenicity and surface morphology. Thromboresistance decreased in the order of zwitterionomer, anionomer, neutral urethane, and cationomer. Ionization of polyurethanes appears to be a useful technique to improve blood compatibility and to study the role of surface chemistry in artificial surface-induced thrombosis.

Stuart L. Cooper, Ph.D., Principal Investigator
Deane F. Mosher, M.D., Collaborating Investigator
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CASE WESTERN RESERVE UNIVERSITY
Human Vascular Grafts: The Blood/Materials Interaction
GRANT NUMBER: 1 RO1 HL 27277-04

This project is directed toward obtaining a better understanding of the blood/materials interaction in human synthetic vascular grafts. The studies involve human blood interactions with vascular graft materials and the compositional analysis of the pseudointima that develops on human vascular grafts.

Analysis of human pseudointima from Dacron and ePTFE vascular grafts shows a markedly high proportion of type V collagen. Tissue encapsulating human grafts contained types I, III and V collagen, with type I>III>V, as determined by SDS-PAGE of extracts. A pattern of deposition was evident in many prostheses, with a maximal proportion of type V collagen in the pseudointima or inner capsule, and type III in the fabric interstitial tissue. Type I occurred in maximal proportion in tissues most remote from the biomaterial surface, such as in the outer capsule or in fibrous tissue occluding the graft lumen. Type V collagen is non-platelet activating and may be produced as an adaptive healing response to provide a non-endothelialized blood contacting surface with low thrombogenicity.

A recirculating, in vitro system has been used to study the interaction of human blood with vascular graft materials. This system was utilized to evaluate the interaction of platelets with small diameter vascular grafts (4mm ID). The materials tested were NHLBI reference material polydimethylsiloxane (PDMS), NHLBI reference material polyethylene (PE), and expanded polytetrafluoroethylene (ePTFE). Medical grade silicone rubber (SR) tubing was used as a control. The test materials were compared to each other and to the control (SR) to assess platelet activation by each material. Analysis of the results indicated that NHLBI-DTB reference material silica-free polydimethylsiloxane is more platelet activating (as measured by PF4 and βTG release) than NHLBI-DTB reference materials polyethylene, expanded polytetrafluoroethylene, and silicone rubber. NHLBI-DTB reference material polyethylene appears to be the least platelet activating, although all materials are platelet activating as determined by increased PF4 and βTG release, decreased PF3 activity and decreased residual platelet aggregability. Flow-rate studies on 4mm ID expanded polytetrafluoroethylene carried out at flow rates of 100, 75, 50 and 30 ml/min indicate that the most crucial flow rate for platelet activation is 50 ml/min. This is significant as it is in the flow rate range for clinical utilization of these materials. Furthermore, these results support the efficacy of this system in determining the thrombogenicity of candidate cardiovascular materials.

James M. Anderson, M.D., Ph.D., Principal Investigator

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BROWN UNIVERSITY
Bioresorbable Vascular Prostheses
GRANT NUMBER: 5 R01 HL 28975-03

Our research hypothesis is that the elements of the natural arterial wall can be reorganized through natural repair processes if the scaffold of a vascular graft is made of a slowly disappearing, nontoxic polymer yarn. The general objective of the project is to explore the feasibility of blood conduits which at the time of implantation display the mechanical strength, suturability, and limited thrombogenicity of standard vascular grafts, but lead, after disappearance of a bioresorbable polymer fabric, to the advent of a newly formed vessel wall of appropriate strength and hemocompatibility, without at any time allowing the rupture of the arterial wall.

The experience of the first 2 years of this project has shown that an aortic graft made entirely of bioresorbable materials is indeed feasible and can function effectively in a canine model for at least 6 months. At that point, the synthetic fabric has decayed to a substantial extent and no longer contributes to the function of the graft. A newly formed internal capsule provides the mechanical integrity of the conduit. However, the healing process has not stabilized, and no stable time end point has yet been reached.

The objectives for the second phase of this project are: (a) to optimize yarn configuration, weaving patterns, coating materials, and coating techniques for incorporation into fully bioresorbable vascular grafts; (b) to screen polymer yarns, fabrics, and coatings through subcutaneous implants in mice and dogs in order to evaluate durability and repair processes; (c) to evaluate such prostheses in the infrarenal aortic position in the dog and to establish the time course of the morphologic and mechanical landmarks of the progressive replacement of the polymer structures by living tissues; (d) to extend the histological, chemical, and engineering information to the point of complete stabilization of the process; (e) and to broaden the concept of bioresorbable scaffolds to confront unmet needs in vascular surgery, such as atrial and vascular patches, small diameter arterial prostheses, and venous prostheses.

Pierre M. Galletti, M.D., Ph.D., Principal Investigator
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MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL
Effects of Compliance Mismatch in Arterial Grafts
GRANT NUMBER: 5 R01 HL 29429-03

The objective of this project is to conclusively demonstrate or rule out compliance as a significant influence on graft patency. This is to be accomplished by comparing grafts with different mechanical properties but identical flow surfaces. Such grafts were produced from canine carotid arteries using a technique of differential fixation with glutaraldehyde. The surfaces of the two conduits were shown to be equivalent by scanning electron microscopy, infrared spectroscopy and measurements of critical surface tension.

When inserted bilaterally in the femoral artery of dogs, the compliant graft remained patent almost universally while the incompliant graft had a tendency to become occluded after 2 to 8 weeks; this trend was not statistically significant, however. In the presence of a highly thromboresistant surface, demonstrating the importance of graft compliance has proved elusive. Additional studies to determine the influence of compliance mismatch in the presence of more challenging flow surfaces are ongoing.

The possible relationship between PHZ, the perianastomotic hypercompliance zone (wherein the compliance of artery first increases before dropping to a minimum as one approaches an anastomotic suture line), and subintimal hyperplasia at the anastomoses, a cause of frequent graft failure, is also under study, as is the cause of PHZ. For this purpose, we have developed an in vitro model of an arterial anastomosis, with which average pressure and diameter can be more carefully controlled, in the absence of systemically induced changes in smooth muscle tone.

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UNIVERSITY OF WASHINGTON
Mechanisms of Arterial Graft Failure
GRANT NUMBER: 5 R01 HL 30946-03

In synthetic arterial prostheses, endothelial coverage is generally obtained by ingrowth of cells from the cut edges of adjacent artery. We have previously demonstrated this mechanism of repair in standard PTFE grafts (30 μm internodal distance--Gore-Tex). In this study, we have investigated the possibility that endothelial coverage of a graft might be achieved not only by ingrowth from the ends but also by transmural penetration of capillaries. For the purposes of this study, we made use of PTFE grafts of higher porosity (60 μm internodal distance). Using a previously described baboon aortoiliac graft model, we studied the repair processes in these permeable grafts. Four millimeter grafts, 6-9 cm in length, were inserted in the aortoiliac system and retrieved at intervals between 1 week and 3 months. All animals received tritiated thymidine, and the grafts were fixed by perfusion fixation. Endothelial coverage was documented by scanning microscopy, hautchen preparations combined with factor VIII staining and transmission microscopy. In summary, our initial observations indicate: (1) rapid coverage of the entire luminal surface by endothelial cells beginning in some grafts as early as 1 week after surgery and complete in all grafts at 1 month, (2) transmural ingrowth of the capillary buds providing multiple sources of endothelium, (3) microvascular orifices all along the graft at 2-4 weeks which disappear for the most part by 3 months, and (4) transmural communication between the graft lumen and vessels in the perigraft granulation tissue by means of these microvessels. Thymidine autoradiography on all en face preparations demonstrated high levels of endothelial proliferation along the entire graft even at late times. Intimal thickening developed uniformly along these grafts only after the times. Intimal thickening developed uniformly along these grafts only after the endothelial layer had been established. By ultrastructural, histochemical, and immunohistological criteria, the cells of the intima were smooth muscle cells and appeared to be derived from pericytes accompanying the transmural growth of microvessels.

These observations indicate that there are at least two possible mechanisms of endothelial repair in vascular grafts. Whether endothelial coverage by the capillary mechanism is a property of all porous grafts or is a mechanism of repair found only in baboons remains yet to be determined.

Alexander W. Clowes, M.D., Principal Investigator
Michael A. Reidy, Ph.D., Collaborating Investigator

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UNIVERSITY OF VIRGINIA
Extending the Life of Aortic Bioprostheses
GRANT NUMBER: 5 R01 HL 31478-02

The purpose of this project is to design new bioprosthetic valves which will duplicate the geometry and function of the natural aortic valve. Bioprostheses are made in various designs and materials. Since all cardiac bioprostheses are meant to perform the function of natural cardiac valves, their short functional life may be the result of failure to duplicate the design of the natural valve. We are presently preparing new porcine and pericardial valves. The design of the natural aortic valve is described in terms of Rc (radius of a circle through three commissures), Rb (radius of a circle through three bases), H (valve height), (angle of leaflet free edge), and (angle of bottom surface of the leaflet). These design parameters change during a cardiac cycle. To begin with, we selected Rc, Rb, and H at mid-diastole, then a mandrel was prepared which will fit the stents of these dimensions. At this point, we decided to proceed with the stent that is closest to this design. In the near future, new stents of the exact design will be prepared. For the leaflets, another mandrel was made so as to maintain them in a fully open position. The neutral position of the leaflet during tissue fixation must be flat. To achieve this for the porcine valve, another three-legged device was made.

To make a porcine bioprosthetic valve, porcine aortic valves were harvested. A three-legged device was inserted in the valve, and the leaflets were allowed to become flat. The valve was fixed at zero pressure. The leaflet mandrel was inserted in the valve so as to obtain circular configuration of the leaflet. The aortic root, with the leaflet mandrel in place, was sewn inside the stent. The valve is functioning well 15 days after implantation in a calf. To prepare a pericardial valve, the pericardium was fixed flat. The leaflet mandrel was positioned on the stent, and the leaflets were sewn in place so that the valve had fully open configuration. This valve was implanted in a calf 21 days ago and seems to be functioning beautifully.

In the future, more work will be done in two areas: (1) making more valves and (2) determining the optimal valve design. Several more stent and leaflet mandrels will be made so that exact valve dimensions can be achieved. Valves will be made from flexible as well as rigid stents. For fixation of the leaflet, various methods will be tried so that the mechanical properties of the leaflets are similar to those of the natural aortic valve. Since it is not possible to duplicate all of the designs and properties of the natural aortic valve in bioprosthetic valves, the question of which parameters are more critical has to be addressed. To resolve this, we will prepare a computer program of the basic design of a bioprosthetic valve. Using this program, a change in any given design parameter will be produced, and the effect of this change on the behavior of the valve will be predicted. Valve longevity will be evaluated in terms of valve degeneration and calcification.

Mano J. Thubrikar, Ph.D., Principal Investigator
Stanton P. Nolan, M.D., Collaborating Investigator

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LOYOLA UNIVERSITY MEDICAL CENTER AND HINES VETERANS ADMINISTRATION HOSPITAL
Application of Arterial Regeneration
GRANT NUMBER: 5 RO1 HL32340-02

Analyses were performed on the histologic, ultrastructural, and functional characteristics of tissue regenerated in vivo over woven absorbable poly-dioxanone (PDS) prostheses and compared with earlier results using more rapidly absorbed polymeric and/or dacron prostheses.

Twenty eight PDS prostheses, 4mm I.D. x 24mm length, were interposed into rabbit aortas. Resultant prosthesis/tissue complexes were explanted after 2 weeks to 1 year. Specimens were evaluated grossly, photographed, and sectioned for light microscopy and scanning and transmission electron microscopy. Pulsatile compliance characteristics and contents of 6-keto-$PGF_{1\alpha}$ and thromboxane B_2 in regenerated tissues were assayed.

No thromboses or hemorrhages were seen. Smooth tissue conduits formed in 27/28 (96 percent) with 1/28 (4 percent) aneurysm and no stenoses. The kinetics of tissue regeneration, as in all other evaluated absorbable arterial prostheses, reflected the rate of material resorption, with tissue thickening from 2 weeks to 3 months after PDS implantation and then stabilizing.

Intra-cytoplasmic PDS inclusions within macrophages and giant cells were seen at 2 weeks, coincidental with the infiltration of the interstices and inner capsules (IC) with primitive mesenchymal cells. Capillary invasion of IC tissues was extensive. By 3 months, specimens were composed of a 420μ thick IC of numerous oriented smooth muscle-like myofibroblasts beneath a confluent endothelial-like luminal surface. The cellular surface was maintained throughout the 12 month period.

Regenerated tissues displayed arterial-like elastic characteristics. 6-keto-$PGF_{1\alpha}$ content of PDS IC tissues (17 ± 8 pg/0.1cc or .37 ± .14 pg/μg total protein) were significantly lower than normal controls (33 ± 7 pg/0.1cc or 1.45 ± .33 pg/μg total protein) but significantly greater than dacron containing prosthesis groups (6.3 ± 1.3 pg/0.1cc or .09 ± 0.02 pg/μg total protein) lacking the cellular flow surface. The 6-keto-$PGF_{1\alpha}/TxB_2$ ratio in PDS ICs (1.44 ± .63) did not differ significantly from normal controls (1.69 ± .54) but significantly greater than the corresponding ratio in dacron containing prosthesis groups (.24 ± .08).

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UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
Endothelial Cell Harvesting for Vascular Prosthetic Seeding
GRANT NUMBER: 1 RO1 HL33931-01

The goal of this study is to devise a reliable, efficient method of enzymatic endothelial cell (EC) harvesting from small segments of adult human peripheral veins which uses defined mixtures of purified enzymes to dissociate EC from the subendothelial basement membrane. To estimate the number of viable EC harvested per cm^2 vein lumen we plated primary EC harvests into replicate fibronectin-coated microwell cultures to derive the EC plating number from counts of attached EC during the initial stationary phase of the growth curve. Scanning E.M. study of vein segments perfusion fixed with silver nitrate border staining at normal dimensions gave a baseline estimate of available in situ EC density of 1.2 ± 0.3 (SD) X 10^5 EC/cm^2 vein lumen (N=4 SEM fields from 4 veins). The microwell method was used to compare a Crude Harvest Solution (CHS) of 0.1 percent crude CLSII collagenase with 0.5 percent BSA in Ca++ and Mg++ free PBS (PBS-CMF) to a Partially Purified Harvest Solution (P1HS). The latter employed CLSII from the same lot as CHS which had been partially purified on a hydroxyapatite column and then adjusted to a concentration (0.85 percent) which gave a basement membrane lysis activity (BMLA) equal to that of the CHS. BMLA was assayed as radiation released from a suspension of finely ground ^3H-acetylated bovine anterior lens capsule particles chosen as a partial mimic of type IV-collagen-containing subendothelial basement membrane.

Saphenous vein segments, excised by conventional dissection, all showed partial preharvest EC desquamation on SEM. In a series of 19 vein harvests (six with CHS, 8 with P1HS, and five with enzyme free control HS) all enzymatic EC harvests grew to produce cofluent homogeneous EC cultures identified by LDL uptake stains. Control enzyme-free harvests gave no significant EC yield or growth. CHS and P1HS gave statistically similar mean respective harvest efficiencies of 16 and 13 percent of the morphometric SEM estimate of available EC. P1HS, however, caused significantly less destruction of human fibronectin measured by a monoclonal-based ELISA, and also caused less alteration of EC luminal surfaces in an aggregometry assay employing microcarrier beads covered with confluent EC. These initial results suggest that (1)partially purified enzymes or defined mixtures of completely purified enzymes, adjusted to BMLA equivalence, may inflict less EC damage than crude collagenase without a loss of viable EC yield, and (2) that vein excision methods which better preserve the EC layer by using papaverine infiltration around the vein may also increase the EC yield.

An additional finding of this work was that standard surgical glove powder shed into EC suspensions releases 0.2 micron filterable material(s), which may be either vulcanization accelerators or endotoxin, which are toxic to EC cultures. This problem can be avoided by using radiation-sterilized particle-free latex gloves.

John B. Sharefkin, M.D., Principal Investigator
Harold E. Van Wart, Ph.D., Collaborating Investigator

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Therapeutic Instrumentation and Devices

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MASSACHUSETTS INSTITUTE OF TECHNOLOGY
A Program for the Management of Heart Failure
CONTRACT NUMBER: 5 R01 HL 33041-02

The overall objective of this research is to develop a methodology for assisting the physician in reasoning about the diagnosis and management of disease, particularly when causality, physiological relationships, and changes over time are important to the reasoning process. The context for this research is heart failure--a problem which requires a thorough understanding of the hemodynamic and physiological relationships of the cardiovascular system for effective management. Our approach to the problem is to organize the program as a series of modules acting on a central, partially constrained causal model of the cardiovascular system representing what is known about the patient. The various modules take input from the user to constrain the model, do diagnostic reasoning from the model, reason about possible therapies, and produce explanations from the model.

Over the past year, the focus of our research has been reasoning about the possible effects of therapies once the state of the patient is determined by interpretation of the findings and diagnostic reasoning. Since the constrained model represents the state and relationship between physiological parameters in the patient, the strategy is to propagate the implied perturbations of therapies through the model to predict the changes to important parameters. The situation is complicated by the large number of both negative and positive feedback loops in the model. Our strategy is to assume that the relationships between parameters can be modeled as piece-wise linear. Thus, the model can be represented by a set of linear differential equations. If we further assume that for the time intervals of interest the system reaches a steady state, the techniques of signal flow analysis are relevant to determining the expected effects of therapies.

We have taken the algorithm implied by Mason's general gain formula for signal flow graphs and modified it to compute the gain from a perturbation at all other parameters, rather than the gain between a single input and single output. The algorithm is then used to predict the direction and relative amount of change in the physiological parameters. These changes are then used to predict which parameters are likely to change qualitative states and therefore move the model into a different linear region. The algorithm, along with tools for highlighting pathways that make the strongest contribution to particular parameter changes, appears to provide a useful mechanism for predicting and justifying the effects of therapy.

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CASE WESTERN RESERVE UNIVERSITY
Defibrillator Waveshape Optimization
GRANT NUMBER: 5 R01 HL 24606-06

During cardiac defibrillation, it is desirable to use the minimum shock intensity which will reliably defibrillate in order to decrease shock-induced dysfunction and to allow the production of smaller, less expensive defibrillators. Our previous studies suggested that biphasic waveforms could decrease defibrillation threshold as well as ameliorating shock-induced dysfunction.

In order to define threshold reducing parameters for biphasic waveforms and to determine the mechanism by which these waveforms decrease threshold, we used a model system consisting of cultured myocardial cell aggregates. Excitation thresholds were examined for symmetrical, rectangular biphasic waveforms having equal amplitudes in the positive and negative portions under conditions of uniform external field stimulation in 21 cultures. Strength-duration curves for these waveforms were compared with similar curves for control monophasic rectangular waveforms having durations equal to those of the positive portion of the biphasic waveforms.

The results showed a significant reduction in threshold for biphasic waveforms. The rheobase for the biphasic waveform was 61 percent that of the monophasic waveform. The chronaxies for both waveforms were similar. The bi-monophasic ratio derived from these curves decreased with increasing duration.

Since the currently accepted hypothesis is that defibrillation is achieved by exciting a critical mass of tissue, rendering the tissue refractory, and interrupting the circus movement, these results suggest that modifications in waveform can reduce the current or energy required for clinical defibrillation.

Janice L. Jones, Ph.D., Principal Investigator
Ronald E. Jones, M.S.E.E., Collaborating Investigator

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CASE WESTERN RESERVE UNIVERSITY
Defibrillator-Induced Dysfunction
GRANT NUMBER: 5 R01 HL 26924-05

The deleterious effects of cardiac defibrillation, including electrocardiographic changes, A-V block, and a low percent success, appear to be related to shock-induced dysfunction at the level of the individual myocardial cell. The specific cellular alterations, contracture, cell-to-cell uncoupling, and mitochondrial changes suggest that calcium overload may be an underlying dysfunction mechanism. In order to test this hypothesis, we are determining the degree and time course of calcium overload following electric field stimulation of different intensities and waveforms in a cultured myocardial cell model using the newly developed calcium indicator, Quin 2. Quin 2 diffuses into cells as the nonpolar tetraacetoxymethyl ester and is hydrolyzed by endogenous esterases to the nonpermeant tetracarboxylate anion which is trapped in the cell and buffers calcium. The intensity of fluorescence is a function of intracellular calcium.

Experiments were carried out in 13 preparations to determine optimal loading conditions. Intracellular calcium in resting cells was 1.34×10^{-7} M as measured in a fluorometer. Ionomycin, a calcium agonist (N = 15), and ouabain, a cardiac glycoside (N = 2), produced a dose-dependent increase in intracellular calcium. Digitonin produced a dose-dependent corelease of Quin 2 and LDH, a cytoplasmic enzyme, demonstrating that Quin 2 is localized in the cytoplasm (N = 5).

Following electric field stimulation at 200 V/cm with a 5 msec rectangular waveform, an increased intracellular fluorescence intensity was observed microscopically. The intensity increased over a period of 40 seconds and corresponded to a developing postshock contracture. Following multiple shocks, fluorescence intensity was proportional to shock number.

These results show that the newly developed calcium indicator Quin 2 can be used to determine intracellular calcium concentration in isolated myocardial cells and that these cells have cytosolic calcium concentrations within the range observed for other cell types. The results also suggest that cytosolic calcium increases following high-intensity electric shock and that this increase may underlie postshock dysfunction.

Janice L. Jones, Ph.D., Principal Investigator
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PRITZKER INSTITUTE OF MEDICAL ENGINEERING
ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO
Closed-Loop Implantable Antiarrhythmic Drug Infusion
GRANT NUMBER: 1 R01 HL 32131-01A1

A growing number of drugs, devices, and surgical techniques are available for treating patients with paroxysmal tachycardia, and the likelihood of successfully managing these patients is steadily increasing. Still, the available therapies are associated with considerable risks, inconvenience, and inefficacy, and new strategies for treating arrhythmias are needed. We believe that a significant potential role exists for an implantable device which would be capable of detecting arrhythmias and of responding by delivering a pharmacokinetically based infusion of an antiarrhythmic drug.

During the past year, we have developed a system for optimal infusion which utilizes two-compartment pharmacokinetics and consists of an initial dose to achieve the desired target plasma level in the central compartment followed by an exponentially decreasing intravenous infusion to maintain this plasma level, ending at the conventional maintenance rate. We studied three mongrel dogs in a series of experiments using procainamide. A bolus infusion and constant drip were applied, blood samples were assayed, and a nonlinear regression analysis was performed to determine each animal's pharmacokinetic parameters. Then, 4 days later, an exponential infusion was performed, based on those parameters.

We have concluded from these preliminary experiments and from our extensive computer simulation studies that exponential infusion gives lower initial overshoot and quicker response than bolus plus drip when both are based on normal pharmacokinetic parameters, even though the animal's parameters vary from normal. If pharmacokinetic characterization can be done in advance of implantation, and also during followup, the opportunity for safe and effective drug management is even better.

Robert Arzbaecher, Ph.D., Principal Investigator
Thomas Bump, M.D., Co-Principal Investigator
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Charles Yurkonis, M.S., Co-Investigator

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CRI, LTD.
Development of an Angulation Mechanism for Catheters and Angioscopes
GRANT NUMBER: 1 R43 HL 33051-01

Science has progressed to the point that catheters and angioscopes can be used for the direct visualization of interior surfaces of the heart and coronary. The primary hindrance to further progress in this field is the lack of a miniaturized angulation system. Our research offers tne definitive answer to this problem.

The concept uses high-technology plastics and a proprietary angulation technique. The miniaturized angulation system is incorporated into the wall of a catheter tip to provide approximately 180° single axis movement. The angulation mechanism is controlled using a low-voltage DC power supply coupled through an electronic control mechanism. Our studies have shown that this technique provides very precise distal tip control.

Using a prototype catheter, a cardiac catheterization was performed on a canine model. Under standard fluoroscopy, a catheter incorporating the angulation mechanism was introduced using standard cut down of the right femoral artery. The catheter was advanced into the lower aorta without the benefit of a guide wire. The angulation mechanism was manipulated, and the catheter was advanced into the left ventricle then withdrawn and manipulated into a coronary artery. During the entire procedure, continuous cardiac monitoring of rhythm strips and hemodynamics were observed. Particular attention was given to rhythm strips when the angulation system was activated. Pathological examination was conducted on the circulation system including microscopy and electromicroscopy of vessel walls. Special attention was focused upon perforation, dissection, and clot formation. The results indicated that the angulation technology as it stands is safe for use in the circulation system of a canine model.

Being able to accurately angulate or steer the distal tip of a catheter or angioscope while in the body has important applications in all types of catheterization procedures performed today. The ability to precisely place drugs, electrical charged microinstrumentation, and light using minimally invasive techniques should have broad application throughout medical research. Many inventors have recognized this need, however, there are no existing techniques that provide the great deal of precision or microminiaturization that this technology promises.

William C. McCoy, Principal Investigator

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NU-TECH INDUSTRIES, INC.
Portable High Frequency Ventilatory Assister
GRANT NUMBER: 1 R43 HL 34256-01

High frequency jet ventilation is beneficial in the clinical treatment of pulmonary edema, adult respiratory distress syndrome, cardiopulmonary resuscitation and penetrating chest wall injuries. However, because current assisters are designed only for hospital critical care use, they are bulky, complicated to operate, and not intended for portability. Therefore, patient use is typically temporary, immobilizing and limited to critical condition cases.

The technologies of small pneumatic pumps, miniature brushless DC motors, integrated electronics, and high energy density batteries are being combined to construct a light weight and portable high frequency ventilatory assister capable of providing extended, personal ventilation assist to the patient suffering chronic pulmonary disease. The first unit will be constructed using commercially available components and will be evaluated in human trials to test the capability of jet ventilation in treating the active (mobile) patient. After the tests prove the unit's potential capability, future development will include the optimization and special design of the system components and configuration.

The portable assister's fully developed configuration, plus its high reliability and simple control features, will make the unit available to patients on a long term and unsupervised basis without the sacrifice of their mobility. The unit will provide the chronic obstructive pulmonary disease patient with 5 to 10 liters per minute of extra ventilation without increasing the work of breathing on the part of the patient.

Milton S. Isaacson, BSEE, PE, Principal Investigator
Gregory A. Thompson, Test Lab Supervisor
Richard A. Krumholz, M.D., Investigator
Roger L. Summers, MSME, PE, Consultant

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CONTROL DYNAMICS COMPANY
The Design of a Closed-Loop Digital Control System for Canine Heart Rate
GRANT NUMBER: 1 R43 HL GM 34270-01

Using the drug esmolol, a fast acting, beta-1 adrenergic blocking agent, it is possible to control tachycardia in patients during general anesthesia and postoperatively. The design of a computerized system capable of the automated management of tachycardia using closed-loop infusion of the drug esmolol has been proposed.

The canine model was chosen to define the transfer function characteristics of the system. Ten animals were given randomly ordered bolus dose levels of esmolol and their heart rate (HR) responses measured. Data from 21 of the 34 boluses administered were used to derive the general mathematical model. Using the definition of the Z-transform, frequency responses were derived from the experimental time responses measured. Transfer functions relating the bolus input of the drug esmolol to the effects of the injection on HR were formulated in terms of the Laplace transform variable s from the frequency response data derived. A generalized mathematical model was formulated which included HR variability. A time domain simulation based on the mathematical model was implemented, the output of which matched closely the actual time responses obtained in the animal experiments.

Using digital domain techniques exclusively, a digital controller was designed. The efficacy of the controller has been demonstrated in the canine simulation. Planned future work involves the implementation in hardware and software of the digital HR controller and the testing of the system in the animal model. Upon verification of the function of the controller in the dog, the model is planned to be modified for human subjects and the controller refined for use in postoperative patients.

Sherman M. Seltzer, Ph.D., Principal Investigator
Angelia P. Bukley, M.S., Collaborating Investigator
Joseph G. Reeves, M.D., Collaborating Investigator

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Appendix

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PRIMARY REFERENCE MATERIALS
PROGRAM OVERVIEW

The Devices and Technology Branch of the National Heart, Lung, and Blood Institute has been making available Primary Reference Materials to qualified investigators in blood-materials interactions. This is being done in order to facilitate comparison of results obtained in different institutions and research laboratories or at different times. Two polymers are available: low density polyethylene and polydimethylsiloxane. These are highly purified, well characterized materials supplied sterile as packaged sheets and small diameter tubes with detailed handling instructions which include recommended storage conditions.

These Primary Reference Materials are to be used to qualify experimental methods or secondary working materials. It is expected that each institution or laboratory will choose and maintain a working reference, the use of which will allow valid comparisons either of candidate methods for evaluating blood-material interactions or of candidate plymers. Periodic comparison of the selected secondary reference material with the Primary Reference Material will insure against undetected changes in both the experimental methods and the secondary reference. In addition, measurement of the physiochemical properties of both the secondary standard and the well characterized Primary Reference Material will allow comparisons of measurements in different laboratories.

It is recognized that the sheet and tube forms and dimensions available may not be suited for a number of biological evaluations. In such cases, the secondary standard should be selected so as to be formable both as sheets and tubes for comparison with the Primary Reference Materials and in the form needed for the particular experimental protocol being used.

In order to make these Primary Reference Materials of most value to the blood-materials research community, it is requested that all recipients report the data obtained in their evaluation and characterization of both the primary and secondary standards directly to the NHLBI Program Office.

A request form is attached to facilitate procurement of Primary Reference Materials by interested investigators. The completed forms may be either deposited in the box provided for this purpose during the DTB Contractors Meeting in the display area, or mailed directly to:

Primary Reference Materials Program
Devices and Technology Branch, DHVD
National Heart, Lung, and Blood Institute
Federal Building
7550 Wisconsin Avenue
Bethesda, MD 20205

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PRIMARY REFERENCE MATERIALS

REQUEST FORM

Investigator: _____ Date: _____

Title: _____

Institution: _____

Address: _____

_____

Telephone: _____

A. Primary Reference Material(s) requested:

1. Type: Low Density Polyethylene Supplier: ABIOMED

☐ Sheets, quantity: _____

☐ Tubes, quantity: _____, Length: _____

2. Type: Polydimethylsiloxane Supplier: MERCOR, INC. (THORATEC)

☐ Sheets, quantity: _____

☐ Tubes, quantity: _____, Length: _____

B. Proposed Secondary Reference Material (if applicable): _____

C. HHS Grant or Contract Number (if applicable): _____

D. Brief description of research for which Primary Reference Material is requested:

_____

_____

_____

It is understood that data obtained from use of the requested Primary Reference Materials will be transmitted to: Primary Reference Materials Program, Devices and Technology Branch, NHLBI, Federal Building, 7550 Wisconsin Avenue, Bethesda, MD 20205.

Agreed: _____
(Signature)

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